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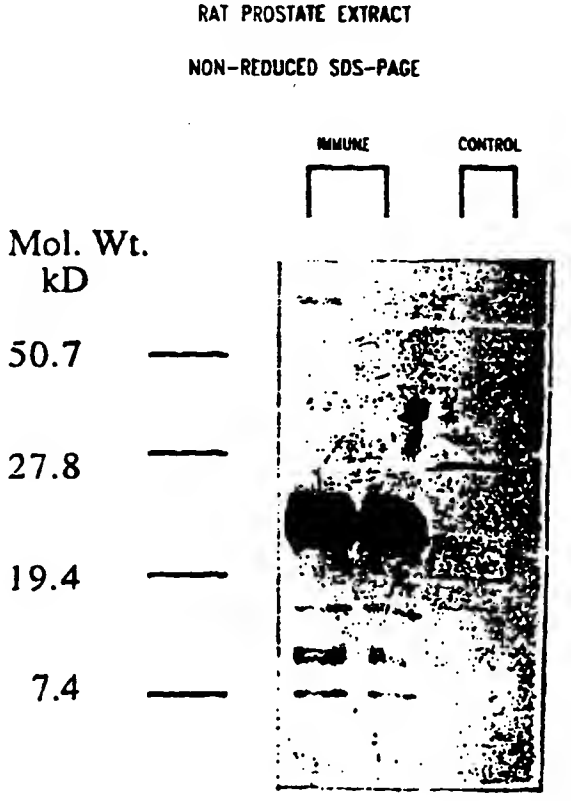
(54) Title: COMPOUNDS AND METHODS FOR IMMUNOTHERAPY AND IMMUNODIAGNOSIS OF PROSTATE CANCER

(57) Abstract

Compounds and methods for treating and diagnosing prostate cancer are provided. The inventive compounds include polypeptides containing at least a portion of a prostate protein. Vaccines and pharmaceutical compositions for immunotherapy of prostate cancer comprising such polypeptides or DNA molecules encoding such polypeptides are also provided. The inventive polypeptides may also be used to generate antibodies useful for the diagnosis and monitoring of prostate cancer. Nucleic acid sequences for preparing probes, primers, and polypeptides are also provided.



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COMPOUNDS AND METHODS FOR IMMUNOTHERAPY AND IMMUNODIAGNOSIS OF PROSTATE CANCER

TECHNICAL FIELD

The present invention relates generally to the treatment, diagnosis and monitoring of prostate cancer. The invention is more particularly related to polypeptides comprising at least a portion of a prostate protein. Such polypeptides may be used in vaccines and pharmaceutical compositions for treatment of prostate cancer. The polypeptides may also be used for the production of compounds, such as antibodies, useful for diagnosing and monitoring the progression of prostate cancer, and possibly other tumor types, in a patient.

BACKGROUND OF THE INVENTION

Prostate cancer is the most common form of cancer among males, with an estimated incidence of 30% in men over the age of 50. Overwhelming clinical evidence shows that human prostate cancer has the propensity to metastasize to bone, and the disease appears to progress inevitably from androgen dependent to androgen refractory status, leading to increased patient mortality. This prevalent disease is currently the second leading cause of cancer death among men in the U.S.

In spite of considerable research into therapies for the disease, prostate cancer remains difficult to treat. Commonly, treatment is based on surgery and/or radiation therapy, but these methods are ineffective in a significant percentage of cases. Three prostate specific proteins - prostate specific antigen (PSA) and prostatic acid phosphatase (PAP) - have limited diagnostic and therapeutic potential. PSA levels do not always correlate well with the presence of prostate cancer, being positive in a percentage of non-prostate cancer cases, including benign prostatic hyperplasia (BPH). Furthermore, PSA measurements correlate with prostate volume, and do not indicate the level of metastasis.

Accordingly, there remains a need in the art for improved vaccines and diagnostic methods for prostate cancer.

SUMMARY OF THE INVENTION

The present invention provides compounds and methods for immunotherapy and diagnosis of prostate cancer. In one aspect, polypeptides are provided comprising at least an immunogenic portion of a prostate protein having a partial sequence as provided in SEQ ID NOS: 2 and 4-8, or a variant of such a protein that differs only in conservative substitutions and/or modifications, together with polypeptides comprising an immunogenic portion of a prostate protein, or a variant thereof, wherein the protein comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of sequences recited in SEQ ID NOS: 11, 13-19, 58, 59 and 61-64, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID NOS: 11, 13-19, 58, 59 and 61-64, or a complement thereof under moderately stringent conditions.

In related aspects, DNA molecules encoding the above polypeptides, expression vectors comprising such DNA molecules and host cells transformed or transfected with such expression vectors are also provided. In preferred embodiments, the host cells are selected from the group consisting of *E. coli*, yeast and mammalian cells.

The present invention also provides pharmaceutical compositions comprising one or more of the polypeptides of SEQ ID NOS: 1-8, 20, 21, 25-31, 44-57, 60 or 61, or DNA molecules of SEQ ID NOS: 9-19, 22-24, 32-43, 58, 59 or 61-64 and a physiologically acceptable carrier. The invention further provides vaccines comprising one or more of such polypeptides or DNA molecules in combination with a non-specific immune response enhancer.

In yet another aspect, methods are provided for inhibiting the development of prostate cancer in a patient, comprising administering an effective amount of one or more of the polypeptides of SEQ ID NOS: 1-8, 20, 21, 25-31, 44-57, 60 or 61, or DNA molecules of SEQ ID NOS: 9-19, 22-24, 32-43, 58, 59 or 61-64 to a patient in need thereof.

In further aspects, methods are provided for detecting prostate cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that is capable of binding to a polypeptide of SEQ ID NOS: 1-8, 20, 21, 25-31, 44-57, 60 or 61; and (b) detecting in the sample a protein or polypeptide that binds to the binding agent.

In related aspects, methods are provided for monitoring the progression of prostate cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that is capable of binding to a polypeptide of SEQ ID NOS: 1-8, 20, 21, 25-31, 44-57, 60 or 61; (b) determining in the sample an amount of a protein or polypeptide that binds to the binding agent; (c) repeating steps (a) and (b); and comparing the amounts of polypeptide detected in steps (b) and (c).

Within related aspects, the present invention provides antibodies, preferably monoclonal antibodies, that bind to the polypeptides described above, as well as diagnostic kits comprising such antibodies, and methods of using such antibodies to inhibit the development of prostate cancer.

The present invention also provides methods for detecting prostate cancer comprising: (a) obtaining a biological sample from a patient; (b) contacting the sample with at least two oligonucleotide primers in a polymerase chain reaction, at least one of the oligonucleotide primers being specific for a DNA sequence selected from the group consisting of SEQ ID NOS: 9-19, 22-24, 32-43, 58, 59 and 61-64; and (c) detecting in the sample a DNA sequence that amplifies in the presence of the oligonucleotide primer. In one embodiment, the oligonucleotide primer comprises at least about 10 contiguous nucleotides of a DNA sequence selected from the group consisting of SEQ ID NOS: 9-19, 22-24, 32-43, 58, 59 and 61-64.

In a further aspect, the present invention provides a method for detecting prostate cancer in a patient comprising: (a) obtaining a biological sample from the patient; (b) contacting the sample with an oligonucleotide probe specific for a DNA sequence selected from the group consisting of SEQ ID NOS: 9-19, 22-24, 32-43, 58, 59 and 61-64; and (c) detecting in the sample a DNA sequence that hybridizes to the oligonucleotide probe. In one embodiment, the oligonucleotide probe comprises at

least about 15 contiguous nucleotides of a DNA sequence selected from the group consisting of SEQ ID NOS: 9-19, 22-24, 32-43, 58, 59 and 61-64.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 illustrates a Western blot analysis of sera obtained from rats immunized with rate prostate extract.

Fig. 2 illustrates a non-reduced SDS PAGE of the rat immunizing preparation of Fig. 1.

Fig. 3 illustrates the binding of a putative human homologue of rat steroid binding protein to progesterone and to estramustine.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the immunotherapy, diagnosis and monitoring of prostate cancer. The inventive compositions are generally polypeptides that comprise at least a portion of a human prostate protein, the protein demonstrating immunoreactivity with human prostate sera. Also included within the present invention are molecules (such as an antibody or fragment thereof) that bind to the inventive polypeptides. Such molecules are referred to herein as "binding agents."

In particular, the subject invention discloses polypeptides comprising at least a portion of a human prostate protein provided in SEQ ID NOS: 2 and 4-8, or a variant of such a protein that differs only in conservative substitutions and/or modifications. As used herein, the term "polypeptide" encompasses amino acid chains of any length, including full length proteins, wherein the amino acid residues are linked by covalent peptide bonds. Thus, a polypeptide comprising a portion of one of the above prostate proteins may consist entirely of the portion, or the portion may be

present within a larger polypeptide that contains additional sequences. The additional sequences may be derived from the native protein or may be heterologous, and such sequences may be immunoreactive and/or antigenic.

As used herein, an "immunogenic portion" of a human prostate protein is a portion that reacts either with sera derived from an individual inflicted with autoimmune prostatitis or with sera derived from a rat model of autoimmune prostatitis. In other words, an immunogenic portion is capable of eliciting an immune response and as such binds to antibodies present within prostatitis sera. Autoimmune prostatitis may occur, for example, following treatment of bladder cancer by administration of Bacillus Calmette-Guerin (BCG), an avirulent strain of *Mycobacterium bovis*. In the rat model of autoimmune prostatitis, rats are immunized with a detergent extract of rat prostate. Sera from either of these sources may be used to react with the human prostate derived polypeptides described herein. Antibody binding assays may generally be performed using any of a variety of means known to those of ordinary skill in the art, as described, for example, in Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1988. For example, a polypeptide may be immobilized on a solid support (as described below) and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ^{125}I-labeled Protein A.

The compositions and methods of the present invention also encompass variants of the above polypeptides and DNA molecules. A polypeptide "variant," as used herein, is a polypeptide that differs from the recited polypeptide only in conservative substitutions and/or modifications, such that the therapeutic, antigenic and/or immunogenic properties of the polypeptide are retained. Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most preferably at least about 95% identity to the identified polypeptides as determined using the computer algorithm FASTX employing default parameters. For prostate tumor polypeptides with immunoreactive properties, variants may, alternatively, be identified by modifying the amino acid sequence of one of the above polypeptides, and evaluating

the immunoreactivity of the modified polypeptide. For prostate tumor polypeptides useful for the generation of diagnostic binding agents, a variant may be identified by evaluating a modified polypeptide for the ability to generate antibodies that detect the presence or absence of prostate cancer. Such modified sequences may be prepared and tested using, for example, the representative procedures described herein.

As used herein, a "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. In general, the following groups of amino acids represent conservative changes: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his.

Variants may also, or alternatively, contain other modifications, including the deletion or addition of amino acids that have minimal influence on the antigenic properties, secondary structure and hydropathic nature of the polypeptide. For example, a polypeptide may be conjugated to a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (*e.g.*, poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

A nucleotide "variant" is a sequence that differs from the recited nucleotide sequence in having one or more nucleotide deletions, substitutions or additions. Such modifications may be readily introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis as taught, for example, by Adelman et al. (*DNA, 2*:183, 1983). Nucleotide variants may be naturally occurring allelic variants, or non-naturally occurring variants. Variant nucleotide sequences preferably exhibit at least about 70%, more preferably at least about 80% and most preferably at least about 90% identity to the recited sequence. Such variant nucleotide sequences will generally hybridize to the recited nucleotide sequence under

stringent conditions. As used herein, "stringent conditions" refers to prewashing in a solution of 6X SSC, 0.2% SDS; hybridizing at 65 °C, 6X SSC, 0.2% SDS overnight; followed by two washes of 30 minutes each in 1X SSC, 0.1% SDS at 65 °C and two washes of 30 minutes each in 0.2X SSC, 0.1% SDS at 65 °C.

Polypeptides having one of the sequences provided in SEQ ID NOS: 1 to 8, 20, 21 and 25-31 may be isolated from a suitable human prostate adenocarcinoma cell line, such as LnCap.fgc (ATCC No. 1740-CRL). LnCap.fgc is a prostate adenocarcinoma cell line that is a particularly good representation of human prostate cancer. Like the human cancer, LnCap.fgc cells form progressively growing tumors as xenografts in SCID mice, respond to testosterone, secrete PSA and respond to the presence of bone marrow components (*e.g.*, transferrin). In particular, the polypeptides may be isolated by expression screening of a LnCap.fgc cDNA library with human prostatitis sera using techniques described, for example, in Sambrook et al., *Molecular Cloning: A Laboratory Manual,* Cold Spring Harbor Laboratories, Cold Spring Harbor, NY (and references cited therein), and as described in detail below. The polypeptides of SEQ ID NOS: 48 and 49 may be isolated from the LnCap/fgc cell line by screening with sera from the rat model of autoimmune prostatitis discussed above. The polypeptides of SEQ ID NOS: 50-56 may be isolated from the LnCap/fgc cell line by screening with human prostatitis sera as described in detail in Example 4. The polypeptides of SEQ ID NOS: 44-47 may be isolated from human seminal fluid as described in detail in Example 2. The polypeptides encoded by the sequences of SEQ ID NOS: 58 and 59 may be isolated by screening a prostate tumor cDNA expression library with monkey anti-prostate sera as detailed below in Example 6. Polypeptides encoded by the cDNA sequences of SEQ ID NO: 61-66 may be isolated by screening a prostate tumor cell-line expression library with a prostate tumor-specific monoclonal antibody. Once a DNA sequence encoding a polypeptide is obtained, any of the above modifications may be readily introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis.

The polypeptides disclosed herein may also be generated by synthetic or recombinant means. Synthetic polypeptides having fewer than about 100 amino acids,

and generally fewer than about 50 amino acids, may be generated using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. *See* Merrifield, *J. Am. Chem. Soc. 85*:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Applied BioSystems, Inc., (Foster City, CA), and may be operated according to the manufacturer's instructions.

Alternatively, any of the above polypeptides may be produced recombinantly by inserting a DNA sequence that encodes the polypeptide into an expression vector and expressing the protein in an appropriate host. Any of a variety of expression vectors known to those of ordinary skill in the art may be employed to express recombinant polypeptides of this invention. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line, such as CHO cells. The DNA sequences expressed in this manner may encode naturally occurring polypeptides, portions of naturally occurring polypeptides, or other variants thereof.

In general, regardless of the method of preparation, the polypeptides disclosed herein are prepared in substantially pure form (*i.e.*, the polypeptides are homogenous as determined by amino acid composition and primary sequence analysis). Preferably, the polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. In certain preferred embodiments, described in more detail below, the substantially pure polypeptides are incorporated into pharmaceutical compositions or vaccines for use in one or more of the methods disclosed herein.

In a related aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, a polypeptide of the present invention and a known prostate antigen, together with variants of such

fusion proteins. The fusion proteins of the present invention may also include a linker peptide between the first and second polypeptides.

A DNA sequence encoding a fusion protein of the present invention is constructed using known recombinant DNA techniques to assemble separate DNA sequences encoding the first and second polypeptides into an appropriate expression vector. The 3' end of a DNA sequence encoding the first polypeptide is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide so that the reading frames of the sequences are in phase to permit mRNA translation of the two DNA sequences into a single fusion protein that retains the biological activity of both the first and the second polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptides by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene 40*:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA 83*:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may be from 1 to about 50 amino acids in length. Peptide sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding

the first polypeptides. Similarly, stop codons require to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Polypeptides of the present invention that comprise an immunogenic portion of a prostate protein may generally be used for immunotherapy of prostate cancer, wherein the polypeptide stimulates the patient's own immune response to prostate tumor cells. In further aspects, the present invention provides methods for using one or more of the immunoreactive polypeptides disclosed herein (or DNA encoding such polypeptides) for immunotherapy of prostate cancer in a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may be afflicted with a disease, or may be free of detectable disease. Accordingly, the above immunoreactive polypeptides may be used to treat prostate cancer or to inhibit the development of prostate cancer. The polypeptides may be administered either prior to or following surgical removal of primary tumors and/or treatment by administration of radiotherapy and conventional chemotherapeutic drugs.

In these aspects, the polypeptide is generally present within a pharmaceutical composition and/or a vaccine. Pharmaceutical compositions may comprise one or more polypeptides, each of which may contain one or more of the above sequences (or variants thereof), and a physiologically acceptable carrier. The vaccines may comprise one or more of such polypeptides and a non-specific immune response enhancer, such as an adjuvant, biodegradable microsphere (*e.g.*, polylactic galactide) or a liposome (into which the polypeptide is incorporated). Pharmaceutical compositions and vaccines may also contain other epitopes of prostate cell antigens, either incorporated into a combination polypeptide (*i.e.*, a single polypeptide that contains multiple epitopes) or present within a separate polypeptide.

Alternatively, a pharmaceutical composition or vaccine may contain DNA encoding one or more of the above polypeptides, such that the polypeptide is generated *in situ*. In such pharmaceutical compositions and vaccines, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression

systems. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter). Bacterial delivery systems involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an epitope of a prostate cell antigen on its cell surface. In a preferred embodiment, the DNA may be introduced using a viral expression system (*e.g.*, vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., *PNAS 86*:317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci. 569*:86-103, 1989; Flexner et al., *Vaccine 8*:17-21, 1990; U.S. Patent Nos.NOS 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques 6*:616-627, 1988; Rosenfeld et al., *Science 252*:431-434, 1991; Kolls et al., *PNAS 91*:215-219, 1994; Kass-Eisler et al., *PNAS 90*:11498-11502, 1993; Guzman et al., *Circulation 88*:2838-2848, 1993; and Guzman et al., *Cir. Res. 73*:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in published PCT application WO 90/11092, and Ulmer et al., *Science 259*:1745-1749, 1993, reviewed by Cohen, *Science 259*:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

Routes and frequency of administration, as well as dosage, will vary from individual to individual and may parallel those currently being used in immunotherapy of other diseases. In general, the pharmaceutical compositions and vaccines may be administered by injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. Between 1 and 10 doses may be administered over a 3-24 week period. Preferably, 4 doses are administered, at an interval of 3 months, and booster administrations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of polypeptide or DNA that is effective to raise an immune response (cellular and/or humoral) against prostate tumor cells in a treated

patient. A suitable immune response is at least 10-50% above the basal (*i.e.*, untreated) level. In general, the amount of polypeptide present in a dose (or produced *in situ* by the DNA in a dose) ranges from about 1 pg to about 100 mg per kg of host, typically from about 10 pg to about 1 mg, and preferably from about 100 pg to about 1 μg. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.01 mL to about 5 mL.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax and/or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and/or magnesium carbonate, may be employed. Biodegradable microspheres (*e.g.*, polylactic glycolide) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

Any of a variety of non-specific immune response enhancers may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a nonspecific stimulator of immune response, such as lipid A, *Bordella pertussis* or *Mycobacterium tuberculosis*. Such adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI) and Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ).

Polypeptides disclosed herein may also be employed in *ex vivo* treatment of prostate cancer. For example, cells of the immune system, such as T cells, may be isolated from the peripheral blood of a patient, using a commercially available cell separation system, such as CellPro Incorporated's (Bothell, WA) CEPRATE™ system (see U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). The separated cells are stimulated with one or more of

the immunoreactive polypeptides contained within a delivery vehicle, such as a microsphere, to provide antigen-specific T cells. The population of tumor antigen-specific T cells is then expanded using standard techniques and the cells are administered back to the patient.

Polypeptides of the present invention may also, or alternatively, be used to generate binding agents, such as antibodies or fragments thereof, that are capable of detecting metastatic human prostate tumors.

Binding agents of the present invention may generally be prepared using methods known to those of ordinary skill in the art, including the representative procedures described herein. Binding agents are capable of differentiating between patients with and without prostate cancer, using the representative assays described herein. In other words, antibodies or other binding agents raised against a prostate protein, or a suitable portion thereof, will generate a signal indicating the presence of primary or metastatic prostate cancer in at least about 20% of patients afflicted with the disease, and will generate a signal indicating the absence of the disease in at least about 90% of individuals without primary or metastatic prostate cancer. Suitable portions of such prostate proteins are portions that are able to generate a binding agent that indicates the presence of primary or metastatic prostate cancer in substantially all (*i.e.*, at least about 80%, and preferably at least about 90%) of the patients for which prostate cancer would be indicated using the full length protein, and that indicate the absence of prostate cancer in substantially all of those samples that would be negative when tested with full length protein. The representative assays described below, such as the two-antibody sandwich assay, may generally be employed for evaluating the ability of a binding agent to detect metastatic human prostate tumors.

The ability of a polypeptide prepared as described herein to generate antibodies capable of detecting primary or metastatic human prostate tumors may generally be evaluated by raising one or more antibodies against the polypeptide (using, for example, a representative method described herein) and determining the ability of such antibodies to detect such tumors in patients. This determination may be made by assaying biological samples from patients with and without primary or metastatic

prostate cancer for the presence of a polypeptide that binds to the generated antibodies. Such test assays may be performed, for example, using a representative procedure described below. Polypeptides that generate antibodies capable of detecting at least 20% of primary or metastatic prostate tumors by such procedures are considered to be able to generate antibodies capable of detecting primary or metastatic human prostate tumors. Polypeptide specific antibodies may be used alone or in combination to improve sensitivity.

Polypeptides capable of detecting primary or metastatic human prostate tumors may be used as markers for diagnosing prostate cancer or for monitoring disease progression in patients. In one embodiment, prostate cancer in a patient may be diagnosed by evaluating a biological sample obtained from the patient for the level of one or more of the above polypeptides, relative to a predetermined cut-off value. As used herein, suitable "biological samples" include blood, sera, urine and/or prostate secretions.

The level of one or more of the above polypeptides may be evaluated using any binding agent specific for the polypeptide(s). A "binding agent," in the context of this invention, is any agent (such as a compound or a cell) that binds to a polypeptide as described above. As used herein, "binding" refers to a noncovalent association between two separate molecules (each of which may be free (*i.e.*, in solution) or present on the surface of a cell or a solid support), such that a "complex" is formed. Such a complex may be free or immobilized (either covalently or noncovalently) on a support material. The ability to bind may generally be evaluated by determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind" in the context of the present invention when the binding constant for complex formation exceeds about 10^3 L/mol. The binding constant may be determined using methods well known to those of ordinary skill in the art.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome with or without a peptide component,

an RNA molecule or a peptide. In a preferred embodiment, the binding partner is an antibody, or a fragment thereof. Such antibodies may be polyclonal, or monoclonal. In addition, the antibodies may be single chain, chimeric, CDR-grafted or humanized. Antibodies may be prepared by the methods described herein and by other methods well known to those of skill in the art.

There are a variety of assay formats known to those of ordinary skill in the art for using a binding partner to detect polypeptide markers in a sample. *See*, *e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In a preferred embodiment, the assay involves the use of binding partner immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a second binding partner that contains a reporter group. Suitable second binding partners include antibodies that bind to the binding partner/polypeptide complex. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding partner after incubation of the binding partner with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding partner is indicative of the reactivity of the sample with the immobilized binding partner.

The solid support may be any material known to those of ordinary skill in the art to which the antigen may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the antigen and functional groups on the support or may be a linkage by way of a cross-linking agent).

Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 μg, and preferably about 100 ng to about 1 μg, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see*, *e.g.*, Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a second antibody (containing a reporter group) capable of binding to a different site on the polypeptide is added. The amount of second antibody that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to

bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is that period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with prostate cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include enzymes (such as horseradish peroxidase), substrates, cofactors, inhibitors, dyes, radionuclides, luminescent groups, fluorescent groups and biotin. The conjugation of antibody to reporter group may be achieved using standard methods known to those of ordinary skill in the art.

The second antibody is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound second antibody is then removed and bound second antibody is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of prostate cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without prostate cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for prostate cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for prostate cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the antibody is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized antibody as the sample passes through the membrane. A second, labeled antibody then binds to the antibody-polypeptide complex as a solution containing the second antibody flows through the membrane. The detection of bound second antibody may then be performed as described above. In the strip test format, one end of the membrane to which antibody is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second antibody and to the area of immobilized antibody. Concentration of second antibody at the area

of immobilized antibody indicates the presence of prostate cancer. Typically, the concentration of second antibody at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of antibody immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1μg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the antigens or antibodies of the present invention. The above descriptions are intended to be exemplary only.

In another embodiment, the above polypeptides may be used as markers for the progression of prostate cancer. In this embodiment, assays as described above for the diagnosis of prostate cancer may be performed over time, and the change in the level of reactive polypeptide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, prostate cancer is progressing in those patients in whom the level of polypeptide detected by the binding agent increases over time. In contrast, prostate cancer is not progressing when the level of reactive polypeptide either remains constant or decreases with time.

Antibodies for use in the above methods may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In one such technique, an immunogen comprising the antigenic polypeptide is initially injected into any of a wide variety of mammals (*e.g.*, mice, rats, rabbits, sheep and goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier

protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for the antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Monoclonal antibodies of the present invention may also be used as therapeutic reagents, to diminish or eliminate prostate tumors. The antibodies may be used on their own (for instance, to inhibit metastases) or coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ^{90}Y, ^{123}I, ^{125}I, ^{131}I, ^{186}Re, ^{188}Re, ^{211}At, and ^{212}Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (*e.g.*, U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise does of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

Diagnostic reagents of the present invention may also comprise DNA sequences encoding one or more of the above polypeptides, or one or more portions thereof. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify prostate tumor-specific cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for a DNA molecule encoding a polypeptide of the present invention. The presence of the amplified cDNA is then detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes specific for a DNA molecule encoding a polypeptide of the present invention may be used in a hybridization assay to detect the presence of an inventive polypeptide in a biological sample.

As used herein, the term "oligonucleotide primer/probe specific for a DNA molecule" means an oligonucleotide sequence that has at least about 80% identity, preferably at least about 90% and more preferably at least about 95%, identity to the DNA molecule in question. Oligonucleotide primers and/or probes which may be usefully employed in the inventive diagnostic methods preferably have at least about 10-40 nucleotides. In a preferred embodiment, the oligonucleotide primers comprise at least about 10 contiguous nucleotides of a DNA molecule encoding one of the polypeptides disclosed herein. Preferably, oligonucleotide probes for use in the inventive diagnostic methods comprise at least about 15 contiguous oligonucleotides of a DNA molecule encoding one of the polypeptides disclosed herein. Techniques for both PCR based assays and hybridization assays are well known in the art (see, for example, Mullis *et al. Ibid*; Ehrlich, *Ibid*). Primers or probes may thus be used to

detect prostate and/or prostate tumor sequences in biological samples, preferably blood, semen or prostate and/or prostate tumor tissue.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 1

A. Isolation of Polypeptides from LnCap.fgc using human prostatitis sera

Representative polypeptides of the present invention were isolated by screening a human prostate cancer cell line with human prostatitis sera as follows. A human prostate adenocarcinoma cDNA expression library was constructed by reverse transcriptase synthesis from mRNA purified from the human prostate adenocarcinoma cell line LnCap.fgc (ATCC No. 1740-CRL), followed by insertion of the resulting cDNA clones in Lambda ZAP II (Stratagene, La Jolla, CA).

Human prostatitis serum was obtained from a patient diagnosed with autoimmune prostatitis following treatment of bladder carcinoma by administration of BCG. This serum was used to screen the LnCap cDNA library as described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989. Specifically, LB plates were overlaid with approximately 10^4 pfu of the LnCap cDNA library and incubated at 42°C for 4 hours prior to obtaining a first plaque lift on isopropylthio-beta-galactoside (IPTG) impregnated nitrocellulose filters. The plates were then incubated for an additional 5 hours at 42°C and a second plaque lift was prepared by incubation overnight at 37°C. The filters were washed three times with PBS-T, blocked for 1 hours with PBS (containing 1% Tween 20™) and again washed three times with PBS-T, prior to incubation with human prostatitis sera at a dilution of 1:200 with agitation overnight. The filters were then washed three times with PBS-T and incubated with ^{125}I-labeled

Protein A (1 µl/15 ml PBS-T) for 1 hour with agitation. Filters were exposed to film for variable times, ranging from 16 hours to 7 days. Plaques giving signals on duplicate lifts were re-plated on LB plates. Resulting plaques were lifted with duplicate filters and these filters were treated as above. The filters were incubated with human prostatitis sera (1:200 dilution) at 4°C with agitation overnight. Positive plaques were visualized with ^{125}I-Protein A as described above with the filters being exposed to film for variable times, ranging from 16 hours to 11 days. *In vivo* excision of positive human prostatitis antigen cDNA clones was performed according to the manufacturer's protocol.

B. Characterization of Polypeptides

DNA sequence for positive clones was obtained using forward and reverse primers on an Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A (Foster City, CA). The cDNA sequences encoding the isolated polypeptides, hereinafter referred to as HPA8, HPA13, HPA15 - HPA17, HPA20, HPA25, HPA28, HPA29, HPA32 - HPA38 and HPA41 are presented in SEQ ID NOS: 32 and 33, 34 and 35, 36, 9 and 10, 11, 12, 13 and 14, 15, 37 and 38, 16, 39, 22 and 23, 17 and 18, 19, 24, 40 and 41, 42 and 43, respectively. The 3' sequences of HPA16 and HPA20 are identical. HPA13, HPA16, HPA20, HPA29 and HPA33 are believed to be overlapping clones with novel 5' end points. Two of the positive clones were determined to be identical to HPA15. Also, HPA15, HPA34 and HPA37 were found to be overlapping clones. The expected N-terminal amino acid sequences of the isolated polypeptides HPA16, HPA17, HPA20, HPA25, HPA28, HPA32, HPA35, HPA36, HPA34, HPA37, HPA8, HPA13, HPA15, HPA29, HPA33, HPA38 and HPA41, based on the determined cDNA sequences in frame with the N-terminal portion of β-galactosidase (lacZ) are presented in SEQ ID NOS: 1-8, 20, 21 and 25-31, respectively.

The determined cDNA and expected amino acid sequences for the isolated polypeptides were compared to known sequences in the gene bank using the EMBL and GenBank (Release 91) databases, and also the DNA STAR system. The DNA STAR system is a combination of the Swiss, PIR databases along with translated

protein sequences (Release 91). No significant homologies to HPA17, HPA25, HPA28, HPA32, HPA35 and HPA36 were found.

The determined cDNA sequence for HPA8 was found to have approximately 100% identity with the human proto-oncogene BMI-1 (Alkema, M.J. et al., *Hum. Mol. Gen. 2*:1597-1603, 1993). Search of the DNA database with 5' and 3' cDNA sequence encoding HPA13 revealed 100% identity with a known cDNA sequence from a human immature myeloid cell line (GenBank Acc. No. D63880). Search of the protein database with the deduced amino acid sequence for HPA13 revealed 100% identity with the open reading frame encoded by the same human cDNA sequence. Search of the protein database with the expected amino acid sequence for HPA15, revealed high homology (60% identity) with a *Saccharomyces cerevisiae* predicted open reading frame (Swiss/PIR Acc. No. S46677), and 100% identity with a human protein from pituitary gland modulating intestinal fluid secretion (Lonnroth, I.., *J. Biol. Chem. 35*:20615-20620, 1995). The deduced amino acid sequence for HPA38 was found to have 100% identity with human heat shock factor protein 2 (Schuetz, T. J. et al., *Proc. Natl. Acad. Sci. USA 88*:6911-6915, 1991). Search of the DNA database with the 5' DNA sequence for HPA41 and search of the protein database with the deduced amino acid sequence revealed 100% identity with a human LIM protein (Rearden, A., *Biochem. Biophys. Res. Commun. 201*:1124-1131, 1994). To the best of the inventors' knowledge, except for LIM protein, none of the inventive polypeptides have been previously shown to be present in human prostate.

Positive phagemid viral particles were used to infect *E. coli* XL-1 Blue MRF', as described in Sambrook et al., *supra*. Induction of recombinant protein was accomplished by the addition of IPTG. Induced and uninduced lysates were run in duplicate on SDS-PAGE and transferred to nitrocellulose filters. Filters were reacted with human prostatitis sera (1:200 dilution) and a rabbit sera (1:200 or 1:250 dilution) reactive with the N-terminal 4 Kd portion of lacZ. Sera incubations were performed for 2 hours at room temperature. Bound antibody was detected by addition of ^{125}I-labeled Protein A and subsequent exposure to film for variable times ranging from 16

hours to 11 days. The results of the immunoblots are summarized in Table I, wherein (+) indicates a positive reaction and (-) indicates no reaction.

TABLE I

Antigen	Human Prostatitis Sera	Anti-lacZ Sera	Protein Mass/Kd
HPA8	(-)	(-)	
HPA13	(+)	(+)	
HPA15	(+)	(+)	50
HPA16	(+)	(+)	40
HPA17	(+)	(-)	40
HPA20	(+)	(+)	38
HPA25	(-)	(+)	32
HPA28	(-)	(-)	
HPA29	(+)	(+)	
HPA32	(-)	(-)	
HPA33	(+)	(+)	
HPA34	not tested	(+)	50
HPA35	(-)	(-)	
HPA36	(-)	(-)	
HPA37	not tested	(+)	50
HPA38	(-)	(-)	
HPA41	not tested	(+)	

Positive reaction of the recombinant human prostatitis antigens with both the human prostatitis sera and anti-lacZ sera indicate that reactivity of the human prostatitis sera is directed towards the fusion protein. Cloned antigens showing reactivity to the human prostatitis sera but not to anti-lacZ sera indicate that the reactive protein is likely initiating within the clone. Antigens reactive with the anti-lacZ sera

but not with the human prostatitis sera may be the result of the human prostatitis sera recognizing conformational epitopes, or the antigen-antibody binding kinetics may be such that the 2 hour sera exposure in the immunoblot is not sufficient. Antigens not reactive with either sera are not being expressed in *E. coli*, and reactive epitopes may be within the fusion protein or within an internal open reading frame. Due to the instability of recombinant antigens from HPA13, HPA29 and HPA33, it was not possible to determine the size of the recombinant antigens.

The expression of representative human prostatitis antigens was investigated by RT-PCR in four different human cell lines (including two metastatic prostate tumor lines LNCaP and DU145), normal prostate, breast, colon, kidney, stomach, lung and skeletal muscle tissue, nine different prostate tumor samples and three different breast tumor samples. The results of these studies are shown in Table II.

Table II

Analysis of HPA clone mRNA expression by RT-PCR in human cell lines, normal tissues and tumors

Clone	LNCaP	DU145	MCF-12A	HBL-100	Prostate	Breast	Colon	Kidney	Stomach	Lung	Skel. Muscle
hpa-17	+	++	+	+	+	-	±	-	-	+	+
hpa-20	+++	++++	NT	NT	±	NT	NT	-	NT	+	NT
hpa-28	+	+++	+	+	+	-	±	+	-	+	±

	Prostate Tumors (n=9)									Breast Tumors (n=3)		
Clone	Tumor 1	Tumor 2	Tumor 3	Tumor 4	Tumor 5	Tumor 6	Tumor 7	Tumor 8	Tumor 9	Tumor 1	Tumor 2	Tumor 3
hpa-17	+	+	+	-	+	+	±	-	-	+	++	++
hpa-20	+	+	NT	NT	NT	NT	NT	NT	NT	+	+	+++
hpa-28	+	+	±	-	+	+	++	±	-	++	+++	+

mRNA expression of representative antigens in LNCaP and normal prostate, kidney, liver, stomach, lung and pancreas was also investigated by RNase protection. The results of these studies are provided in Table III.

Table III

Analysis of HPA clone mRNA expression by RNase protection in LNCaP and normal human tissues

Clone	LNCaP	Prostate	Kidney	Liver	Stomach	Lung	Pancreas
hpa-15	+	-	++	++	+	-	++
hpa-20	+++++	+	+	+	+	NT	NT
hpa-25	+	+	+	+	++	++	NT
hpa-32	NT	++	+	+	NT	++	NT
hpa-35	+++	+++	NT	+	+	+++	+
hpa-36	+	+	NT	NT	+	+	+

Example 2

A. Isolation and Characterization of Rat Steroid Binding Protein

Immune sera was obtained from rats immunized with rat prostate extract to generate antibodies to self prostate antigens. Specifically, rats were prebled to obtain control sera prior to being immunized with a detergent extract of rat prostate (in PBS containing 0.1% Triton) in Freunds complete adjuvant. A boost of incomplete Freunds adjuvant was given 3 weeks after the initial immunization and sera was harvested at 6 weeks.

The sera thus obtained was subjected to ECL Western blot analysis (Amersham International, Arlington Heights, Ill) using the manufacturer's protocol and a rat prostate protein was identified, as shown in Fig. 1. After reduction, SDS-PAGE revealed a broad silver staining band migrating at 7 kD. Without reduction, a strong band was seen at 24 kD (Fig. 2). This protein was purified by ion exchange

chromatography and subjected to gel electrophoresis under reduced conditions. Three bands were seen, indicating the presence of three chains within the protein: a 6-8 kD chain (C1), a 8-10 kD chain (C2) and a 10-12 kD chain (C3). The protein was further purified by reverse phase HPLC on a Delta™ C18 300 A° 5 μm column, column size 3.9 x 300 mm (Waters-Millipore, Milford, MA). The sample containing 100 μg of protein was dissolved in 0.1% trifluoroacetic acid (TFA), pH 1.9 and polypeptides were eluted with a linear gradient of acetonitrile (0-60%) in 0.1% TFA pH 1.9 at a flow rate of 0.5 mL/min for 1 hour. The eluent was monitored at 214 nm. Two peaks were obtained, a C1-C3 dimer and a C2-C3 dimer. The amino terminus of the C2 chain was found to be blocked. The C1 and C3 chains were sequenced on a Perkin Elmer/Applied Biosystems Inc. Procise Model 494 protein sequencer and found to have the following amino terminal sequences (SEQ ID NOS: 44 and 45, respectively).

(a) Ser-Gln-Ile-Cys-Glu-Leu-Val-Ala-His-Glu-Thr-Ile-Ser-Phe-Leu; and

(b) Xaa-Xaa-Xaa-Xaa-Xaa-Ser-Ile-Leu-asp-Glu-Val-Ile-Arg-Gly-Thr,

wherein Xaa may be any amino acid.

These sequences were compared to known sequences in the gene bank using the databases discussed in Example 1 and were found to be identical to rat steroid binding protein, also known as estramustine-binding protein (EMBP) (Forsgren, B. et al., *Prog. Clin. Biol. Res. 75A*:391-407, 1981; Forsgren, B. et al., *Proc. Natl. Acad. Sci. USA 76*:3149-53, 1979). This protein is a major secreted protein in rat seminal fluid and has been shown to bind steroid, cholesterol and proline rich proteins. EMBP has been shown to bind estramustine and estromustine, the active metabolites of estramustine phosphate. Estramustine phosphate has been found to be clinically useful in treating advanced prostate cancer in patients who do not respond to standard hormone ablation therapy (see, for example, Van Poppel, H. et al., *Prog. Clin. Biol. Res. 370*:323-41, 1991).

B. Isolation of putative human homologue to rat steroid binding protein

Purified rat steroid binding protein was obtained from freshly excised rat prostate and used to subcutaneously immunize a New Zealand white virgin female

rabbit (150 μg purified rat steroid binding protein in 1 ml of PBS and 1 ml of incomplete Freund's adjuvant containing 100 μg of muramyl dipeptide (adjuvant peptide, Calbiochem, La Jolla, CA). Six weeks later the rabbit was boosted subcutaneously with the same protein dose in incomplete Freund's adjuvant. Finally, the rabbit was boosted intravenously two weeks later with 100 μg protein in PBS and the sera harvested two weeks after the final immunization.

The resulting rabbit antisera was used to screen the LnCap.fgc cell line without success. The rabbit antisera was subsequently used to screen human seminal fluid anion exchange chromatography pools using the protocol detailed below in Example 3. This analysis indicated an approximately 18-22 kD cross-reactive protein. The seminal fluid fraction of interest (Fraction 1) was separated into individual components by SDS-PAGE under non-reducing conditions, blotted onto a PVDF membrane, excised and digested with CNBr in 70% formic acid. The resulting CNBr fragments were resolved on a tricine gel system, again electroblotted to PVDF and excised. The sequence for one peptide was determined as follows:

Val-Val-Lys-Thr-Tyr-Leu-Ile-Ser-Ser-Ile-Pro-Leu-Gln-Gly-Ala-Phe-Asn-Tyr-Lys-Tyr-Thr-Ala (SEQ ID NO: 46).

This sequence was compared to known sequences in the gene bank using the databases identified above and was unexpectedly found to be identical to gross cystic disease fluid protein, a protein whose expression was previously found to correlate with the presence of metastatic breast cancer (Murphy, L.C. et al., *J. Biol. Chem. 262*:15236-15241, 1987). To the best of the inventors' knowledge, this protein has not been previously identified in male tissues.

The ability of Fraction 1 as described above, to bind to steroid was investigated as follows. Purified rat steroid binding protein (RSBP) and fraction 1 were subjected to SDS-PAGE and transferred onto nitrocellulose filters. Specifically, 1.5 μg of RSBP/gel lane and 4 μg of fraction 1/gel lane were electrophoresed in parallel on a 4-20% gradient Laemmli gel (BioRad), then electrophoretically transferred to nitrocellulose. After protein transfer, the nitrocellulose was blocked for 1 hour at room temperature in 1% Tween 20 in PBS, rinsed three times for 10 min each

in 10 ml 0.1% Tween 20 in PBS plus 0.5 M NaCl, then probed with either 1) 0.87 μM progesterone conjugated to horseradish peroxidase (HRP, Sigma) diluted in the rinse buffer; 2) 0.87 μM progesterone HRP with 200 μM estramustine; or 3) 0.87 μM progesterone HRP plus 400 μM unlabelled progesterone and 200 μM estramustine. Each reaction mixture was incubated for 1 hour at room temperature and washed three times for 10 min each with 0.1% Tween 20 , PBS, and 0.5 M NaCl. The blots were then developed (ECL system, Amersham) to reveal progesterone HRP binding proteins that are also capable of binding estramustine.

With both rat steroid binding protein and Fraction 1, three bands were obtained that bound HRP-progesterone and that were competed out with unlabelled progesterone and estramustine (Fig. 3). These results indicate that the three bands isolated from human seminal fluid as described above bind hormone and correspond in number of polypeptides to the chains C1, C2 and C3 of rat steroid binding protein, although slightly bigger in size, either due to primary sequence or secondary post-translational modifications.

This putative homologue of rat steroid binding protein was also identified in a subsequent screen of human seminal fluid using the rabbit antisera detailed above. Specifically a hydrophobic 22kD/65kD aggregate protein was obtained which, following CNBr digestion of the 22kD band, provided a peptide having the following sequence:

Val-Val-Lys-Thr-Tyr-Leu-Ile-Ser-Ser-Ile-Pro-Leu-Gln-Ala-Phe-Asn-Tyr-Lys-Tyr-Thr-Ala (SEQ ID NO: 47).

This peptide was found to correspond to residues 67 through 87 of gross cystic disease fluid protein and was identified again utilizing human autoimmune prostatitis sera as discussed below in Example 4.

Example 3

Isolation and Characterization of Polypeptides Isolated from LnCaP.fgc Using Rat Prostatitis Sera

A LnCap.fgc cell pellet was homogenized (10 gm cell pellet in 10 ml) by resuspension in PBS, 1% NP-40 and 60 µg/ml phenylmethylsulfonyl fluoride (PMSF) (Sigma, St. Louis, MO) then 10 strokes in a Dounce homogenizer. This was followed by a 30 second probe sonication and another 10 strokes in the Dounce homogenizer. The resulting slurry was centrifuged at 10,000 x G, and the supernatant filtered with a 0.45 µM filter (Amicon, Beverly, MA) then applied to a BioRad (Hercules, CA) Macro-Prep Q-20 anion exchange resin. Proteins were eluted with a 70 minute 0 to 0.8 M NaCl gradient in 20 mM tris pH 7.5 at a flow rate of 8 ml/min. Fractions were cooled, concentrated with 10 kD MWCO centriprep concentrators (Amicon) and stored at -20°C in the presence of 60 µg/ml PMSF. The ion exchange pools were then examined by electrophoresis on 4-20% tris glycine Ready-Gels (BioRad) and subsequent transfer to nitrocellulose filters. Ion exchange pools of interest were identified by ECL (Amersham International) Western analysis, using the rat sera described above in Example 2A. This analysis indicated an approximately 65 kD protein eluting at 0.08 to 0.13 M NaCl. The rat sera reactive ion exchange pool was subjected to HPLC and subsequent Western analysis to identify the protein fraction of interest. This protein was then digested for 24 hours at 25°C in 70% formic acid saturated with CNBr to cleave at methionine residues.

The resulting CNBr fragments were purified by microbore HPLC using a Vydac C18 column (Hesperia, CA), column size 1x150 mM in a Perkin Elmer/Applied Biosystems Inc. (Foster City, CA) Division Model 172 HPLC. Fractions were eluted from the column with a gradient of 0 to 60% of acetonitrile at a flow rate of 40 µl per minute. The eluent was monitored at 214 nm. The resulting fractions were loaded directly onto a Perkin Elmer/Applied Biosystems Inc. Procise 494 protein sequencer and sequenced using standard Edman chemistry from the amino terminal end. Two different peptides having the following sequences were obtained:

(a) Xaa-Ala-Lys-Lys-Phe-Leu-Asp-Ala-Glu-His-Lys-Leu-Asn-Phe-Ala (SEQ ID NO: 48); and

(b) Xaa-Xaa-Xaa-Lys-Ile-Lys-Lys-Phe-Ile-Gln-Glu-Asn-Ile-Phe-Gly,

wherein Xaa may be any amino acid (SEQ ID NO: 49).

These sequences were compared to known sequences in the gene bank using databases identified above, and identified as residues 286 through 300 and 228 through 242, respectively, of probable protein disulfide isomerase ER-60 precursor, hereinafter referred to as ER-60 (Bado, R. J. et al., *Endocrinology 123*:1264-1273, 1988). This antigen is also known as phospholipase C-alpha (see PCT WO 95/08624). Residues 285 and 227 of ER-60 are methionines, consistent with the above sequences being cyanogen bromide fractions.

ER-60 is a resident endoplasmic protein with multiple biological activities, including disulfide isomerase and restricted cysteine protease activity. In particular, ER-60 has been shown to preferentially degrade calnexin, a protein involved in presentation of antigens via the Class I major histocompatability complex, or MHC, pathway. ER-60 and a related family member, ER-72, have been shown to be over-expressed in colon cancer, with truncated forms of ER-60 exhibiting increased enzymatic activity (Egea, G. et al., *J. Cell. Sci. (England) 105*:819-30, 1993). However, to the best of the inventors' knowledge, this polypeptide has not been previously shown to be present or overexpressed in human prostate. Recently, ER-60 gene expression has been correlated with induction of contact inhibition of cell proliferation (Greene, J.J. et al., *Cell. Mol. Biol. 41*:473-80, 1995). Thus, if ER-60 is also truncated and non-functional in prostate cancer, as it is in colon cancer, the resultant loss of contact inhibition would lead to neoplastic transformation and tumor progression.

Example 4

Isolation and Characterization of Polypeptides Isolated from LnCaP.fgc Using Human Prostatitis Sera

The human prostatitis sera described above in Example 1 was used to screen the LnCaP.fgc cell line using the ion exchange techniques described above in Example 3. Reactive ion exchange pools were purified by reverse phase HPLC as described previously and the polypeptides shown in SEQ ID NOS: 50-56 were isolated utilizing cross-reactivity with said antisera as the selection criteria. Comparison of these sequences with known sequences in the gene bank using the databases described above revealed the homologies shown in Table II. However, none of these polypeptides have been previously associated with human prostate.

TABLE IV

SEQ ID NO:	Database Search Identification
50	glyceraldehyde-3-phosphate-dehydrogenase
51	alpha-human fructose biphosphate aldolase
52	calreticulin
53	calreticulin
54	malate dehydrogenase
55	cystic disease fluid protein
56	cystic disease fluid protein

Example 5

Isolation and Characterization of Polypeptides from Human Seminal Fluid

Polypeptides from human seminal fluid were purified to homogeneity by anion exchange chromatography. Specifically, seminal fluid samples were diluted 1 to 10 with 0.1 mM Bis-Tris propane buffer pH 7 prior to loading on the column. The polypeptides were fractionated into pools utilizing gel profusion chromatography on a Poros (Perseptive Biosystems) 146 II Q/M anion exchange column 4.6 mm x 100 mm equilibrated in 0.01 mM Bis-Tris propane buffer pH 7.5. Proteins were eluted with a linear 0-0.5 M NaCl gradient in the above buffer. The column eluent was monitored at a wavelength of 220 nm. Individual fractions were further purified by reverse phase HLPC on a Vydac (Hesperia, CA) C18 column.

The resulting fractions were sequenced as described above in Example 3. A peptide having the following N-terminal sequence was obtained:

(c) Met-Asp-Ile-Pro-Gln-Thr-Lys-Gln-Asp-Leu-Glu-Leu-Pro-Lys-Leu (SEQ ID NO:57).

Comparison of this sequence with those of known sequences in the gene bank as described above revealed 100% identity with human placental protein 14 (PP14).

Example 6

Isolation of Polypeptides from a Prostate Tumor cDNA Library using Monkey Anti-Prostate Sera

A female cynomologous monkey was immunized with homogenized monkey prostate plus complete Freund's adjuvant. A booster immunization, using the same immunogen, was given one month later. Sera was taken from this monkey two months after the first immunization. This sera was pre-cleared of *E. coli* and phage antigens and used at a 1:200 dilution to screen a primary prostate tumor expression library prepared in Lambda ZAP II (Stratagene).

Two positive clones identified in the screen (hereinafter referred to as JF3 and JF5) were found to be non-sister clones from the same gene. The clones were excised and insert size was determined by restriction digest (JF3 = 1500 bp, JF5 = 1000 bp). Complete DNA sequencing of these clones with both vector and internal primers indicated that the sequence of JF5 was found within that of JF3. Similarly, the partial open reading frame found in JF5 was found to be contained wholly within JF3. The determined cDNA sequences for JF3 and JF5 are provided in SEQ ID NO: 58 and 59, respectively, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 60. Comparison of these sequences with those in the gene bank as described above revealed no significant homologies.

The expression of these antigens in various tissue types was investigated using RT-PCR. Over-expression was found in 2 out of 5 prostate tumor samples, 3 out of 5 normal prostate samples, 1 out of 2 breast tumor samples, and in a normal kidney sample and a normal brain sample. Northern analysis indicated that these antigens may be expressed both in prostate and testis.

Example 7

Isolation of Polypeptides from a Prostate Tumor Cell-Line DNA Library by Expression Screening with Prostate Tumor-Specific Monoclonal Antibodies

This example describes the isolation of polypeptides by screening a human prostate cancer cell line expression library with a monoclonal antibody known as Pro 1.5 as follows.

The Pro 1.5 antibody was generated as follows. High molecular weight DNA from the prostate tumor cell line LnCap was transformed into the non-tumorigenic embryonic rat cell line CREF-6. The transformed cells were then introduced into nude mice. In some cases, the non-tumorigenic CREF cells were able to form tumors in the nude mice because of the presence of the high molecular weight LnCap DNA. These cells were rescued and surface epitope masked using a polyclonal sera generated to non-transformed CREF-6 cells. This sera masks any proteins present on the surface of the non-transformed CREF-6 cells while leaving exposed any proteins

expressed on the surface of the cell due to the presence of the high molecular weight LnCap DNA. These exposed proteins may represent tumor antigens expressed by the transformed CREF-6 cells. The masked cells coated with the anti-CREF-6 antibody were used as an immunogen in immunocompetent mice. After immunization and boosting, the mice were sacrificed and a monoclonal antibody reactive to the transformed cell-line (referred to as Pro 1.5) was generated.

Pro 1.5 was determined to bind to the prostate tumor cell line Du-145 by FACS analysis and was used to screen an unamplified expression library prepared from Du-145 RNA in Lambda ZAP Express (Stratagene). The determined partial cDNA sequences for the first of three genes isolated in this screen are provided in SEQ ID NO: 61 and 62, the determined 5' and 3' sequences for a second clone are provided in SEQ ID NO: 63 and 64, respectively; and the determined partial cDNA sequences for a third isolated clone are provided in SEQ ID NO: 65 and 66. Comparison of these sequences with those in the gene bank revealed no significant homologies to the sequence of SEQ ID NO: 61 and 62. SEQ ID NO: 63 and 64 were found to show some homology to previously isolated expressed sequence tags. The sequence of SEQ ID NO: 65 and 66 were found to represent the known human gene amphiphysin II.

Example 8

Synthesis of Polypeptides

Polypeptides may be synthesized on an Applied Biosystems 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and

lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

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Twardzik, Daniel R.
Mitcham, Jennifer L.

(ii) TITLE OF INVENTION: COMPOUNDS AND METHODS FOR IMMUNOTHERAPY
AND IMMUNODIAGNOSIS OF PROSTATE CANCER

(iii) NUMBER OF SEQUENCES: 66

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(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE: 22-JUN-1998
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 89 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Ala Arg Ala Ser Val Met Leu Leu Gly Met Met Ala Arg Gly Lys Pro
1 5 10 15
Glu Ile Val Gly Ser Asn Leu Asp Thr Leu Met Ser Ile Gly Leu Asp
20 25 30
Glu Lys Phe Pro Gln Asp Tyr Arg Leu Ala Gln Gln Val Cys His Ala
35 40 45
Ile Ala Asn Ile Ser Asp Arg Arg Lys Pro Ser Leu Gly Lys Arg His
50 55 60
Pro Pro Phe Arg Leu Pro Gln Glu His Arg Leu Phe Glu Arg Leu Arg
65 70 75 80
Glu Thr Val Thr Lys Gly Phe Val His
85

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 89 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Ala Arg Gly Arg Phe Gly Arg Leu Gly Val Gly Gly Glu Pro His Pro
1 5 10 15
Arg Arg Asn Pro Ala Leu Pro Thr Glu Leu Ala Glu Leu Thr Pro Gln

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                20                  25                  30
     Val Arg Arg Ala Ala Xaa Lys Thr Gln Arg Ser Gln Val Lys
Pro Arg
            35                  40                  45
     His Arg Arg Gly Trp Pro Pro Thr Val Pro Leu Ala Gly Arg
Leu Glu
        50                  55                  60
     Glu Leu Lys Thr Pro Arg Ser Pro Arg Pro Pro Glu Gln Gly
Leu Asp
     65                  70                  75
80
     Pro Ser Pro Cys Ser Leu Pro Ser Pro
                     85
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(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 858 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

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     Gln Glu Ser Glu Pro Phe Ser His Ile Asp Pro Glu Glu Ser
Glu Glu
     1               5                   10
15
     Thr Arg Leu Leu Asn Ile Leu Gly Leu Ile Phe Lys Gly Pro
Ala Ala
                20                  25                  30
     Ser Thr Gln Glu Lys Asn Pro Arg Glu Ser Thr Gly Asn Met
Val Thr
            35                  40                  45
     Gly Gln Thr Val Cys Lys Asn Lys Pro Asn Met Ser Asp Pro
Glu Glu
        50                  55                  60
     Ser Arg Gly Asn Asp Glu Leu Val Lys Gln Glu Met Leu Val
Gln Tyr
     65                  70                  75
80
     Leu Gln Asp Ala Tyr Ser Phe Ser Arg Lys Ile Thr Glu Ala
Ile Gly
                     85                  90
95
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Ile Ile Ser Lys Met Met Tyr Glu Asn Thr Thr Thr Val Val Gln Glu
100 105 110
Val Ile Glu Xaa Phe Val Met Val Phe Gln Phe Gly Val Pro Gln Ala
115 120 125
Leu Phe Gly Val Arg Arg Met Leu Pro Leu Ile Trp Ser Lys Glu Pro
130 135 140
Gly Val Arg Glu Ala Val Leu Asn Ala Tyr Arg Gln Leu Tyr Leu Asn
145 150 155 160
Pro Lys Gly Asp Ser Ala Arg Ala Lys Ala Gln Ala Leu Ile Gln Asn
165 170 175
Leu Ser Leu Leu Leu Val Asp Ala Ser Val Gly Thr Ile Gln Cys Leu
180 185 190
Glu Glu Ile Leu Cys Glu Phe Val Gln Lys Asp Glu Leu Lys Pro Ala
195 200 205
Val Thr His Leu Leu Trp Glu Arg Ala Thr Glu Lys Val Ala Cys Cys
210 215 220
Pro Leu Glu Arg Cys Ser Ser Val Met Leu Leu Gly Met Met Ala Arg
225 230 235 240
Arg Lys Pro Glu Ile Val Gly Ser Asn Leu Asp Thr Leu Met Ser Ile
245 250 255
Gly Leu Asp Glu Lys Phe Pro Gln Asp Tyr Arg Leu Ala Gln Gln Val
260 265 270
Cys His Ala Ile Ala Asn Ile Ser Asp Arg Arg Lys Pro Ser Leu Gly
275 280 285
Lys Arg His Pro Pro Phe Arg Leu Pro Gln Glu His Arg Leu Phe Glu
290 295 300
Arg Leu Arg Glu Thr Val Thr Lys Gly Phe Val His Pro Asp Pro Leu

305 310 315
320
Trp Ile Pro Phe Lys Glu Val Ala Val Thr Leu Ile Tyr Gln
Leu Ala
325 330
335
Glu Gly Pro Glu Val Ile Cys Ala Gln Ile Leu Gln Gly Cys
Ala Lys
340 345 350
Gln Ala Leu Glu Lys Leu Glu Glu Lys Arg Thr Ser Gln Glu
Asp Pro
355 360 365
Lys Glu Ser Pro Ala Met Leu Pro Thr Phe Leu Leu Met Asn
Leu Leu
370 375 380
Ser Leu Ala Gly Asp Val Ala Leu Gln Gln Leu Val His Leu
Glu Gln
385 390 395
400
Ala Val Ser Gly Glu Leu Cys Arg Arg Arg Val Leu Arg Glu
Glu Gln
405 410
415
Glu His Lys Thr Lys Asp Pro Lys Glu Lys Asn Thr Ser Ser
Glu Thr
420 425 430
Thr Met Glu Glu Glu Leu Gly Leu Val Gly Ala Thr Ala Asp
Asp Thr
435 440 445
Glu Ala Glu Leu Ile Arg Gly Ile Cys Glu Met Glu Leu Leu
Asp Gly
450 455 460
Lys Gln Thr Leu Ala Ala Phe Val Pro Leu Leu Leu Lys Val
Cys Asn
465 470 475
480
Asn Pro Gly Leu Tyr Ser Asn Pro Asp Leu Ser Ala Ala Ala
Ser Leu
485 490
495
Ala Leu Gly Lys Phe Cys Met Ile Ser Ala Thr Phe Cys Asp
Ser Gln
500 505 510
Leu Arg Leu Leu Phe Thr Met Leu Glu Lys Ser Pro Leu Pro
Ile Val

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                515                 520                 525
     Arg Ser Asn Leu Met Val Ala Thr Gly Asp Leu Ala Ile Arg
Phe Pro
          530                 535                 540
     Asn Leu Val Asp Pro Trp Thr Pro His Leu Tyr Ala Arg Leu
Arg Asp
     545                 550                 555
560
     Pro Ala Gln Gln Val Arg Lys Thr Ala Gly Leu Val Met Thr
His Leu
                    565                 570
575
     Ile Leu Lys Asp Met Val Lys Val Lys Gly Gln Val Ser Glu
Met Ala
                580                 585                 590
     Val Leu Leu Ile Asp Pro Glu Pro Gln Ile Ala Ala Leu Ala
Lys Asn
                595                 600                 605
     Phe Phe Asn Glu Leu Ser His Lys Gly Asn Ala Ile Tyr Asn
Leu Leu
          610                 615                 620
     Pro Asp Ile Ile Ser Arg Leu Ser Asp Pro Glu Leu Gly Val
Glu Glu
     625                 630                 635
640
     Glu Pro Phe His Thr Ile Met Lys Gln Leu Leu Ser Tyr Ile
Thr Lys
                    645                 650
655
     Asp Lys Gln Thr Glu Ser Leu Val Glu Lys Leu Cys Gln Arg
Phe Arg
                660                 665                 670
     Thr Ser Arg Thr Glu Arg Gln Gln Arg Asp Leu Ala Tyr Cys
Val Ser
                675                 680                 685
     Gln Leu Pro Leu Thr Glu Arg Gly Leu Arg Lys Met Leu Asp
Asn Phe
          690                 695                 700
     Asp Cys Phe Gly Asp Lys Leu Ser Asp Glu Ser Ile Phe Ser
Ala Phe
     705                 710                 715
720
     Leu Ser Val Val Gly Lys Leu Arg Arg Gly Ala Lys Pro Glu
Gly Lys
                    725                 730
```

735
Ala Ile Ile Asp Glu Phe Glu Gln Lys Leu Arg Ala Cys His
Thr Arg
740 745 750
Gly Leu Asp Gly Ile Lys Glu Leu Glu Ile Gly Gln Ala Gly
Ser Gln
755 760 765
Arg Ala Pro Ser Ala Lys Lys Pro Ser Thr Gly Ser Arg Tyr
Gln Pro
770 775 780
Leu Ala Ser Thr Ala Ser Asp Asn Asp Phe Val Thr Pro Glu
Pro Arg
785 790 795
800
Arg Thr Thr Arg Arg His Pro Asn Thr Gln Gln Arg Ala Ser
Lys Lys
805 810
815
Lys Pro Lys Val Val Phe Ser Ser Asp Glu Ser Ser Glu Glu
Asp Leu
820 825 830
Ser Ala Glu Met Thr Glu Asp Glu Thr Pro Lys Lys Thr Thr
Pro Ile
835 840 845
Leu Arg Ala Ser Ala Arg Arg His Arg Ser
850 855

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 127 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Ala Arg Asp Arg Leu Val Ala Ser Lys Thr Asp Gly Lys Ile
Val Gln
1 5 10
15
Tyr Glu Cys Glu Gly Asp Thr Cys Gln Glu Glu Lys Ile Asp
Ala Leu
20 25 30
Gln Leu Glu Tyr Ser Tyr Leu Leu Thr Ser Gln Leu Glu Ser

```
Gln Arg
            35                  40                  45
     Ile Tyr Trp Glu Asn Lys Ile Val Arg Ile Glu Lys Asp Thr
Ala Glu
         50                  55                  60
     Glu Ile Asn Asn Met Lys Thr Lys Phe Lys Glu Thr Ile Xaa
Xaa Cys
     65                  70                  75
80
     Asp Asn Leu Glu His Xaa Leu Asn Asp Leu Leu Lys Glu Lys
Gln Ser
                    85                  90
95
     Val Glu Arg Lys Cys Thr Gln Leu Asn Thr Lys Val Ala Lys
Leu Thr
                100                 105                 110
     Asn Glu Leu Lys Glu Glu Gln Glu Met Asn Lys Cys Leu Arg
Ala
            115                 120                 125
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(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 43 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

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Arg Arg
     1               5                   10
15
     Arg Ala Gly Gly Asp Gly Gly Asn Ser Gly Ser Cys Ser Arg
Trp Gly
                20                  25                  30
     Gly Phe Thr Ser Tyr Pro Trp Asp Arg Glu Ile
            35                  40
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(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 751 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Pro Ala Glu Ala His Ser Asp Ser Leu Ile Asp Thr Phe Pro Glu Cys
1 5 10 15
Ser Thr Glu Gly Phe Ser Ser Asp Ser Asp Leu Val Ser Leu Thr Val
20 25 30
Asp Val Asp Ser Leu Ala Glu Leu Asp Asp Gly Met Ala Ser Asn Gln
35 40 45
Asn Ser Pro Ile Arg Thr Phe Gly Leu Asn Leu Ser Ser Asp Ser Ser
50 55 60
Ala Leu Gly Ala Val Ala Ser Asp Ser Glu Gln Ser Lys Thr Glu Glu
65 70 75 80
Glu Arg Glu Ser Arg Ser Leu Phe Pro Gly Ser Leu Lys Pro Lys Leu
85 90 95
Gly Lys Arg Asp Tyr Leu Glu Lys Ala Gly Glu Leu Ile Lys Leu Ala
100 105 110
Leu Lys Lys Glu Glu Glu Asp Asp Tyr Glu Ala Ala Ser Asp Phe Tyr
115 120 125
Arg Lys Gly Val Asp Leu Leu Leu Glu Gly Val Gln Gly Glu Ser Ser
130 135 140
Pro Thr Arg Arg Glu Ala Val Lys Arg Arg Thr Ala Glu Tyr Leu Met
145 150 155 160
Arg Ala Glu Ser Ile Ser Ser Leu Tyr Gly Lys Pro Gln Leu Asp Asp
165 170 175
Val Ser Gln Pro Pro Gly Ser Leu Ser Ser Arg Pro Leu Trp Asn Leu

```
                180                 185                 190
     Arg Ser Pro Ala Glu Glu Leu Lys Ala Phe Arg Val Leu Gly
Val Ile
            195                 200                 205
     Asp Lys Val Leu Leu Val Met Asp Thr Arg Thr Glu His Thr
Phe Ile
        210                 215                 220
     Leu Xaa Gly Leu Arg Lys Ser Ser Glu Tyr Ser Arg Asn Arg
Lys Thr
     225                 230                 235
240
     Ile Xaa Pro Arg Cys Val Pro Xaa Met Val Cys Leu His Lys
Tyr Ile
                    245                 250
255
     Ile Ser Glu Glu Ser Xaa Phe Leu Val Leu Gln His Ala Glu
Xaa Gly
                260                 265                 270
     Lys Leu Trp Ser Tyr Ile Ser Lys Phe Leu Asn Arg Ser Pro
Glu Glu
            275                 280                 285
     Ser Phe Asp Ile Lys Glu Val Lys Lys Pro Thr Leu Ala Lys
Val His
        290                 295                 300
     Leu Gln Gln Pro Thr Ser Ser Pro Gln Asp Ser Ser Ser Phe
Glu Ser
     305                 310                 315
320
     Arg Gly Ser Asp Gly Gly Ser Met Leu Lys Ala Leu Pro Leu
Lys Ser
                    325                 330
335
     Ser Leu Thr Pro Ser Ser Gln Asp Asp Ser Asn Gln Glu Asp
Asp Gly
                340                 345                 350
     Gln Asp Ser Ser Pro Lys Trp Pro Asp Ser Gly Ser Ser Ser
Glu Glu
            355                 360                 365
     Glu Cys Thr Thr Ser Tyr Leu Thr Leu Cys Asn Glu Tyr Gly
Gln Glu
        370                 375                 380
     Lys Ile Glu Pro Gly Ser Leu Asn Glu Glu Pro Phe Met Lys
Thr Glu
     385                 390                 395
400
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     Gly Asn Gly Val Asp Thr Lys Ala Ile Lys Ser Phe Pro Ala
His Leu
                    405                 410
415
     Ala Ala Asp Ser Asp Ser Pro Ser Thr Gln Leu Arg Ala His
Glu Leu
                420                 425                 430
     Lys Phe Phe Pro Asn Asp Asp Pro Glu Ala Val Ser Ser Pro
Arg Thr
            435                 440                 445
     Ser Asp Ser Leu Ser Arg Ser Lys Asn Ser Pro Met Glu Phe
Phe Arg
        450                 455                 460
     Ile Asp Ser Lys Asp Ser Ala Ser Glu Leu Leu Gly Leu Asp
Phe Gly
    465                 470                 475
480
     Glu Lys Leu Tyr Ser Leu Lys Ser Glu Pro Leu Lys Pro Phe
Phe Thr
                    485                 490
495
     Leu Pro Asp Gly Asp Ser Ala Ser Arg Ser Phe Asn Thr Ser
Glu Ser
                500                 505                 510
     Lys Val Glu Phe Lys Ala Gln Asp Thr Ile Ser Arg Gly Ser
Asp Asp
            515                 520                 525
     Ser Val Pro Val Ile Ser Phe Lys Asp Ala Ala Phe Asp Asp
Val Ser
        530                 535                 540
     Gly Thr Asp Glu Gly Arg Pro Asp Leu Leu Val Asn Leu Pro
Gly Glu
    545                 550                 555
560
     Leu Glu Ser Thr Arg Glu Ala Ala Ala Met Gly Pro Thr Lys
Phe Thr
                    565                 570
575
     Gln Thr Asn Ile Gly Ile Ile Glu Asn Lys Leu Leu Glu Ala
Pro Asp
                580                 585                 590
     Val Leu Cys Leu Arg Leu Ser Thr Glu Gln Cys Gln Ala His
Glu Glu
            595                 600                 605
     Lys Gly Ile Glu Glu Leu Ser Asp Pro Ser Gly Pro Lys Ser
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Tyr Ser
         610                 615                 620
     Ile Thr Glu Lys His Tyr Ala Gln Glu Asp Pro Arg Met Leu
Phe Val
     625                 630                 635
640
     Ala Xaa Val Asp His Ser Ser Ser Gly Asp Met Ser Leu Leu
Pro Ser
                    645                 650
655
     Ser Asp Pro Lys Phe Gln Gly Leu Gly Val Val Glu Ser Xaa
Val Thr
                660                 665                 670
     Ala Asn Asn Thr Glu Glu Ser Leu Phe Arg Ile Cys Ser Pro
Leu Ser
            675                 680                 685
     Gly Ala Asn Glu Tyr Ile Ala Ser Thr Asp Thr Leu Lys Thr
Glu Glu
         690                 695                 700
     Val Leu Leu Phe Thr Asp Gln Thr Asp Asp Leu Ala Lys Glu
Glu Pro
     705                 710                 715
720
     Thr Ser Leu Phe Xaa Arg Asp Ser Glu Thr Lys Gly Glu Ser
Gly Leu
                    725                 730
735
     Val Leu Glu Gly Asp Lys Glu Ile His Gln Ile Phe Glu Gly
Pro
                740                 745                 750
```

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

```
Ala Arg Gly Ser Thr Gln
1               5
```

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Ala Arg Gly Ser Ser Gln Val Arg Val Lys Ser Trp Arg Gly Asp Met
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 271 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

CCGCACGAGC CTCTGTCATG CTTCTTGGCA TGATGGCACG AGGAAAGCCA GAAATTGTGG 60
GAAGCAATTT AGACACACTG ATGAGCATAG GGCTGGATGA GAAGTTTCCA CAGGACTACA 120
GGCTGGCCCA GCAGGTGTGC CATGCCATTG CCAACATCTC GGACAGGAGA AAGCCTTCTC 180
TGGGCAAACG TCACCCCCCC TTCCGGCTGC CTCAGGAACA CAGGTTGTTT GAGCGACTGC 240
GGGAGACAGT CACAAAAGGC TTTGTCCACC C 271

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 403 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

GGGTGGATAA CCTGAGGTAG GGAGTTCGAG ACCAGCCTGA CCAACATGGA
GAAACCCCAT 60
CTCTACTAAA AATAAAAAAT TAGCCGGCGT ATTGGCGTGC GCCTGTAATC
CCAGCTACTC 120
AAGAGGCTGA GGCAGGAGAA TCGCCTGAAC CCAGAGGCGG AGGTTGTAGT
GAGCCGAAAT 180
CACACCATTG CACTCCAGCT TGGGCAACAA TAGCGAACCT CCATCTCAAA
TTAAAAAAAA 240
AATGCCTACA CGCTTCTTTA AAATGCAAGG CTTTCTCTTA AATTAGCCTA
ACTGAACTGC 300
GTTGAGCTGC TTCAACTTTG GAATATATGT TTGCCAATCT CCTTGTTTTC
TAATGAATAA 360
ATGTTTTTAT ATACTTTTAA AAAAAAAAAA AAAAAAACTC GAG
403

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2276 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GGAGGTTTGG GCGGCTTGGC GTCGGAGGAG AGCCCCACCC GCGGAGGAAC
CCAGCCTTGC 60
CAACGGAGCT GGCGGAGCTC ACTCCTCAGG TCAGGCGGGC GGCGTANAAA
ACGCAGCGGA 120
GCCAGGTGAA ACCAAGGCAC CGCCGTGGCT GGCCCCCGAC AGTTCCTCTA
GCCGGGAGGT 180
TGGAGGAGCT GAAAACGCCG CGGAGCCCTC GGCCGCCCGA GCAGGGGCTG
GACCCCAGCC 240
CTTGCAGCCT CCCTTCTCCT GGCACCCAAG TGCAGTCCTG GCTGCAGAAG
GGGCCGCGGG 300
CGCACTGAGT TTCCAACCTC CGTTCAGCCT GTCTGTCTCA GGGTGCAGCC
TTAATGAGAG 360
GTGATTCCTA AGCTGCTGGG AACCTGAGGT TGTCAAAGGG GCGGCAGGAA
ATGGACAGCA 420
GTATAAAACC CAGAAGCAGA ACTTGAAGGT TAAACCACTA GCCCATTTCA
CAGAATGTTT 480
CATCCATTTG TGGACCAAAA GATGGAGTTG GTTTTTATTT TTAAAAAGAT
AATGTTAATG 540
ATCTGATACC ACTACAAATA TTTACGTGAG AAGATTCATG GACTTGTCTT
TTGGTTGGAC 600

TGTCACTCAT TTCTGAAAGT TTCTTCAGCC ACAATTTCTA TTTGAAAATT
CAAGTATCAA 660
AGGATACCAG GTTTAGAATG GTATAATGAT GTATTTTGTC TGAGGACTGC
AAATTTTATA 720
GAGACCACAG TTGGATTCCA GTGATATTCT GCAATCAAAG TGATTTGATA
AACCTAATTT 780
TGAAGCATTT TATATTTATA AGCGACATCA AAAGATGGGA GAAAAAAATG
GCGATGCAAA 840
AACTTTCTGG ATGGAGCTAG AAGATGATGG AAAAGTGGAC TTCATTTTTG
AACAAGTACA 900
AAATGTGCTG CAGTCACTGA AACAAAAGAT CAAAGATGGG TCTGCCACCA
ATAAAGAATA 960
CATCCAAGCA ATGATTCTAG TGAATGAAGC AACTATAATT AACAGTTCAA
CATCAATAAA 1020
GGATCCTATG CCTGTGACTC AGAAGGAACA GGAAAACAAA TCCAATGCAT
TTCCCTCTAC 1080
ATCATGTGAA AACTCCTTTC CAGAAGACTG TACATTTCTA ACAACAGGAA
ATAAGGAAAT 1140
TCTCTCTCTT GAAGATAAAG TTGTAGACTT TAGAGAAAAA GACTCATCTT
CGAATTTATC 1200
TTACCAAAGT CATGACTGCT CTGGTGCTTG TCTGATGAAA ATGCCACTGA
ACTTGAAGGG 1260
AGAAAACCCT CTGCAGCTGC CAATCAAATG TCACTTCCAA AGACGACATG
CAAAGACAAA 1320
CTCTCATTCT TCAGCACTCC ACGTGAGTTA TAAAACCCCT TGTGGAAGGA
GTCTACGAAA 1380
CGTGGAGGAA GTTTTTCGTT ACCTGCTTGA GACAGAGTGT AACTTTTTAT
TTACAGATAA 1440
CTTTTCTTTC AATACCTATG TTCAGTTGGC TCGGAATTAC CCAAAGCAAA
AAGAAGTTGT 1500
TTCTGATGTG GATATTAGCA ATGGAGTGGA ATCAGTGCCC ATTTCTTTCT
GTAATGAAAT 1560
TGACAGTAGA AAGCTCCCAC AGTTTAAGTA CAGAAAGACT GTGTGGCCTC
GAGCATATAA 1620
TCTAACCAAC TTTTCCAGCA TGTTTACTGA TTCCTGTGAC TGCTCTGAGG
GCTGCATAGA 1680
CATAACAAAA TGTGCATGTC TTCAACTGAC AGCAAGGAAT GCCAAAACTT
CCCCCTTGTC 1740
AAGTGACAAA ATAACCACTG GATATAAATA TAAAAGACTA CAGAGACAGA
TTCCTACTGG 1800
CATTTATGAA TGCAGCCTTT TGTGCAAATG TAATCGACAA TTGTGTCAAA
ACCGAGTTGT 1860
CCAACATGGT CCTCAAGTGA GGTTACAGGT GTTCAAAACT GAGCAGAAGG
GATGGGGTGT 1920
ACGCTGTCTA GATGACATTG ACAGAGGGAC ATTTGTTTGC ATTTATTCAG

GAAGATTACT 1980
AAGCAGAGCT AACACTGAAA AATCTTATGG TATTGATGAA AACGGGAGAG
ATGAGAATAC 2040
TATGAAAAAT ATATTTTCAA AAAAGAGGAA ATTAGAAGTT GCATGTTCAG
ATTGTGAAGT 2100
TGAAGTTCTC CCATTAGGAT TGGAAACACA TCCTAGAACT GCTAAAACTG
AGAAATGTCC 2160
ACCAAAGTTC AGTAATAATC CCAAGGAGCT TACTATGGAA ACGAAATATG
ATAATATTTC 2220
AAGAATTCAG TATCATTCAG TTATTAGAGA TCCTGAATCC AAGACAGCCA TTTTTC
2276

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3114 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

CAGGAGTCCG AACCCTTCAG TCATATAGAC CCAGAGGAGT CAGAGGAGAC
CAGGCTCTTG 60
AATATCTTAG GACTTATCTT CAAAGGCCCA GCAGCTTCCA CACAAGAAAA
GAATCCCCGG 120
GAGTCTACAG GAAACATGGT CACAGGACAG ACTGTCTGTA AAAATAAACC
CAATATGTCG 180
GATCCTGAGG AATCCAGGGG AAATGATGAA CTAGTGAAGC AGGAGATGCT
GGTACAGTAT 240
CTGCAGGATG CCTACAGCTT CTCCCGGAAG ATTACAGAGG CCATTGGCAT
CATCAGCAAG 300
ATGATGTATG AAAACACAAC TACAGTGGTG CAGGAGGTGA TTGAATNCTT
TGTGATGGTC 360
TTCCAATTTG GGGTACCCCA GGCCCTGTTT GGGGTGCGCC GTATGCTGCC
TCTCATCTGG 420
TCTAAGGAGC CTGGTGTCCG GGAAGCCGTG CTTAATGCCT ACCGCCAACT
CTACCTCAAC 480
CCCAAAGGGG ACTCTGCCAG AGCCAAGGCC CAGGCTTTGA TTCAGAATCT
CTCTCTGCTG 540
CTAGTGGATG CCTCGGTTGG GACCATTCAG TGTCTTGAGG AAATTCTCTG
TGAGTTTGTG 600
CAGAAGGATG AGTTGAAACC AGCAGTGACC CATCTGCTGT GGGAGCGGGC
CACCGAGAAG 660
GTCGCCTGCT GTCCTCTGGA GCGCTGTTCC TCTGTCATGC TTCTTGGCAT

GATGGCACGA 720
AGAAAGCCAG AAATTGTGGG AAGCAATTTA GACACACTGA TGAGCATAGG
GCTGGATGAG 780
AAGTTTCCAC AGGACTACAG GCTGGCCCAG CAGGTGTGCC ATGCCATTGC
CAACATCTCG 840
GACAGGAGAA AGCCTTCTCT GGGCAAACGT CACCCCCCCT TCCGGCTGCC
TCAGGAACAC 900
AGGTTGTTTG AGCGACTGCG GGAGACAGTC ACAAAAGGCT TTGTCCACCC
AGACCCACTC 960
TGGATCCCAT TCAAAGAGGT GGCAGTGACC CTCATTTACC AACTGGCAGA
GGGCCCCGAA 1020
GTGATCTGTG CCCAGATATT GCAGGGCTGT GCAAAACAGG CCCTGGAGAA
GCTAGAAGAG 1080
AAGAGAACCA GTCAGGAGGA CCCGAAGGAG TCCCCCGCAA TGCTCCCCAC
TTTCCTGTTG 1140
ATGAACCTGC TGTCCCTGGC TGGGGATGTG GCTCTGCAGC AGCTGGTCCA
CTTGGAGCAG 1200
GCAGTGAGTG GAGAGCTCTG CCGGCGCCGA GTTCTCCGGG AAGAACAGGA
GCACAAGACC 1260
AAAGATCCCA AGGAGAAGAA TACGAGCTCT GAGACCACCA TGGAGGAGGA
GCTGGGGCTG 1320
GTTGGGGCAA CAGCAGATGA CACAGAGGCA GAACTAATCC GTGGCATCTG
CGAGATGGAA 1380
CTGTTGGATG GCAAACAGAC ACTGGCTGCC TTTGTTCCAC TCTTGCTTAA
AGTCTGTAAC 1440
AACCCAGGCC TCTATAGCAA CCCAGACCTC TCTGCAGCTG CTTCACTTGC
CCTTGGCAAG 1500
TTCTGCATGA TCAGTGCCAC TTTCTGCGAC TCCCAGCTTC GTCTTCTGTT
CACCATGCTG 1560
GAAAAGTCTC CACTTCCCAT TGTCCGGTCT AACCTCATGG TTGCCACTGG
GGATCTGGCC 1620
ATCCGCTTTC CCAATCTGGT GGACCCCTGG ACTCCTCATC TGTATGCTCG
CCTCCGGGAC 1680
CCTGCTCAGC AAGTGCGGAA AACAGCGGGG CTGGTGATGA CCCACCTGAT
CCTCAAGGAC 1740
ATGGTGAAGG TGAAGGGGCA GGTCAGTGAG ATGGCGGTGC TGCTCATCGA
CCCCGAGCCT 1800
CAGATTGCTG CCCTGGCCAA GAACTTCTTC AATGAGCTCT CCCACAAGGG
CAACGCAATC 1860
TATAATCTCC TTCCAGATAT CATCAGCCGC CTGTCAGACC CCGAGCTGGG
GGTGGAGGAA 1920
GAGCCTTTCC ACACCATCAT GAAACAGCTC CTCTCCTACA TCACCAAGGA
CAAGCAGACA 1980
GAGAGCCTGG TGGAAAAGCT GTGTCAGCGG TTCCGCACAT CCCGAACTGA
GCGGCAGCAG 2040

CGAGACCTGG CCTACTGTGT GTCACAGCTG CCCCTCACAG AGCGAGGCCT
CCGTAAGATG 2100
CTTGACAATT TTGACTGTTT TGGAGACAAA CTGTCAGATG AGTCCATCTT
CAGTGCTTTT 2160
TTGTCAGTTG TGGGCAAGCT GCGACGTGGG GCCAAGCCTG AGGGCAAGGC
TATAATAGAT 2220
GAATTTGAGC AGAAGCTTCG GGCCTGTCAT ACCAGAGGTT TGGATGGAAT
CAAGGAGCTT 2280
GAGATTGGCC AAGCAGGTAG CCAGAGAGCG CCATCAGCCA AGAAACCATC
CACTGGTTCT 2340
AGGTACCAGC CTCTGGCTTC TACAGCCTCA GACAATGACT TTGTCACACC
AGAGCCCCGC 2400
CGTACTACCC GTCGGCATCC AAACACCCAG CAGCGAGCTT CCAAAAAGAA
ACCCAAAGTT 2460
GTCTTCTCAA GTGATGAGTC CAGTGAGGAA GATCTTTCAG CAGAGATGAC
AGAAGACGAG 2520
ACACCCAAGA AAACAACTCC CATTCTCAGA GCATCGGCTC GCAGGCACAG
ATCCTAGGAA 2580
GTCTGTTCCT GTCCTCCCTG TGCAGGGTAT CCTGTAGGGT GACCTGGAAT
TCGAATTCTG 2640
TTTCCCTTGT AAAATATTTG TCTGTCTCTT TTTTTTAAAA AAAAAAAAGG
CCGGGCACTG 2700
TGGCTCACGC CTGTAATCCC AGCACTTTGC GATACCAAGG CGGGTGGATA
ACCTGAGGTA 2760
GGGAGTTCGA GACCAGCCTG ACCAACATGG AGAAACCCCA TCTCTACTAA
AAATAAAAAA 2820
TTAGCCGGGC GTATTGGCGT GCGCCTGTAA TCCCAGCTAC TCAAGAGGCT
GAGGCAGGAG 2880
AATCGCCTGA ACCCAGAGGC GGAGGTTGTA GTGAGCCGAA ATCACACCAT
TGCACTCCAG 2940
CTTGGGCAAC AATAGCGAAC CTCCATCTCA AATTAAAAAA AAAATGCCTA
CACGCTCTTT 3000
AAAATGCAAG GCTTTCTCTT AAATTAGCCT AACTGAACTG CGTTGAGCTG
CTTCAACTTT 3060
GGAATATATG TTTGCCAATC TCCTTGTTTT CTAATGAATA AATGTTTTTA TATA
3114

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1797 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

CGGCACGAGA TCGACTGGTT GCAAGTAAAA CAGATGGAAA AATAGTACAG
TATGAATGTG 60
AGGGGGATAC TTGCCAGGAA GAGAAAATAG ATGCCTTACA GTTAGAGTAT
TCATATTTAC 120
TAACAAGCCA GCTGGAATCT CAGCGAATCT ACTGGGAAAA CAAGATAGTT
CGGATAGAGA 180
AGGACACAGC AGAGGAAATT AACAACATGA AGACCAAGTT TAAAGAAACA
ATTGAGAAGT 240
GTGATAATCT AGAGCACAAA CTAAATGATC TCCTAAAAGA AAAGCAGTCT
GTGGAAAGAA 300
AGTGCACTCA GCTAAACACA AAAGTGGCCA AACTCACCAA CGAGCTCAAA
GAGGAGCAGG 360
AAATGAACAA GTGTTTGCGA GCCAACCAAG TCCTCCTGCA GAACAAGCTA
AAAGAGGAGG 420
AGAGGGTGCT GAAGGAGACC TGTGACCAAA AAGATCTGCA GATCACCGAG
ATCCAGGAGC 480
AGCTGCGTGA CGTCATGTTC TACCTGGAGA CACAGCAGAA GATCAACCAT
CTGCCTGCCG 540
AGACCCGGCA GGAAATCCAG GAGGGACAGA TCAACATCGC CATGGCCTCG
GCCTCGAGCC 600
CTGCCTCTTC GGGGGGCAGT GGGAAGTTGC CCTCCAGGAA GGGCCGCAGC
AAGAGGGGCA 660
AGTGACCTTC AGAGCAACAG ACATCCCTGA GACTGTTCTC CCTGACACTG
TGAGAGTGTG 720
CTGGGACCTT CAGCTAAATG TGAGGGTGGG CCCTAATAAG TACAAGTGAG
GATCAAGCCA 780
CAGTTGTTTG GCTCTTTCAT TTGCTAGTGT GTGATGTANT GAATGTAAAG
GGTGCTGACT 840
GGAGAGCTGA TAGAAAGGCG CTGCGTTCGA AAAGGTCTTA ANAGTTCACT
AACCTCACAT 900
TCTAATGACC ATTTTGCCTT CCTGCTTGGT AGAAGCCCCA ACTCTGCTGT
GCATTTTTCC 960
ATTGTATTTA TGGAGTTGGC GTATTTGACA TTCAGTTCTG GGGTAGGTTT
AAGATGTTAA 1020
GTTATTTCTT GTAACCTCAA AGGTAAGGTT ATCTAGCACT AAAGCACCAA
ACCTCTCTGA 1080
GGGCATAACA GCTGCTTTAA AGAGAGGTTT CCATTGGCTA TTAAGGAGTT
ATGAAAACTC 1140
CCTAGCAATA GTGTCATATC ATTATCATCT CCCCCTTCCT CTGGGGAGTG
GAAGAATTGC 1200
TTGAATGTTA TCTGAAAAGA GGCCTGGTAG TAAACCAGGC CCTGGCTCTT
TACCAGCAGT 1260
CATCTCTTCT TGCTCTGGGG CCAGCCAGGA AAAACAAACA ACCCGGGGCA

CATTGGGTAG 1320
ACTCAGTGTA GGAAAAATGG TGGCAGCTCC ACTGTTTATT TTTGGTGACT
TCGTACGTCA 1380
TTATGAACCG CAATTAAGGA GGAGGCTTAA TGGCTGTTCC CAAACTCAAA
TCTCAGAGTG 1440
GGTATCCTAG CATCTAGCAA NACTGAGTGG GGAGATTTCT CATCCGTGTG
AAAATGTAGA 1500
GTGAGGCCTC TGACTAGCTN ATTGTGTATT TTGTTGGGTT TAGTATTTTC
TAAATGTTTA 1560
CAAAATATTG GGCTGCATGT TCAGGTTGCA GCTANAGGGA GCTTGGGCAN
ATTTTCAATT 1620
ACGCTTTCAA GATATAACCA AAAGCTGTTT CTAAATCCTA AAATTAGAAT
TTCAACAGAN 1680
CCCCCTTTAG AACAGTCATA TAACGCTTGT GTGGGCCAAC AGANGGGCTG
TGTACTCTCT 1740
CTGGAACCAT AAATGTCAAA TAATTTATAA CCTGCANTAA TTGAGCAACT TAAATAA
1797

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 720 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

TAATCACCAT CTGTTTTTGT GGGATGTGCT GCAGCATTTC CCAAAAAACT
TNACGTGTAA 60
TGTTGCAAAA TGAATGTACT CAGACATTNT TAATTTTTAC TTAGGGCAGA
CCAACTCTTT 120
GAGTCTCTCT TGGACTTATA TATACAGATA TCTTAAGAGT GGGAATGTAA
AGCATAACCT 180
AATTNTCTTT CCTATAGAGA TTCTATTTTA TTTAAAATNT ATTTNTACAC
TAGTTAGAAT 240
CCTGCTGTTT TGGCCAAGTA CTTGTCTTGC ATGTCTGACC TTGCAGAAGC
TGGGGTGGAT 300
CATAGCATAC TAATGAAGAG AATTAGAAGT AGTTTACAAA GCTCGCTCAC
TCCTCATTTC 360
TCTGTGATCC CTTCTATCCA GTGGCCCCAC CACCACCTGG GAAAACAGAT
TTTTCAGTAC 420
AGGTGGGATA AATGCTCTGA AAGGCTGTGC CCAGAGGAAT GAGCAAATAG
GCAAGTGTTT 480
CCAAACTACT TGGAGGTTTA CAAAAAATAT GTCCCAGAAA AAAAAAAAAT

CTTACCAAGA 540
TACGTAAAGA AAAAAAAATT TTTTTTTAAA CAGTCAAAGA GTCATGTTTG
AATTTCACAA 600
AATCACATCA GACAGAAGTT GTTTTCTTCA GGAGGGAAAT GAACCACTTA
ATATACCCAT 660
ACTACCTTGA ACAATGAAAT TGAATTAAAA TAGCCAAACT TTGAAAAAAA
AAAAAAAAAA 720

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1996 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

CAGAAGTGCA GCGGTGGCGG CGGCTGGTTG CGGGCCGGCG GCGGGCTGGC
GGAGATGGAG 60
GTAACTCAGG ATCTTGTTCA AGATGGGGTG GCTTCACCAG CTACCCCTGG
GACCGGGAAA 120
TCTAAGCTGG AAACATTGCC CAAAGAAGAC CTCATCAAGT TTGCCAAGAA
ACAGATGATG 180
CTAATACAGA AAGCTAAATC AAGGTGTACA GAATTGGAGA AAGAAATTGA
AGAACTCAGA 240
TCAAAACCTG TTACTGAAGG AACTGGTGAT ATTATTAAGG CATTAACTGA
ACGTCTGGAT 300
GCTCTTCTTC TGGAAAAAGC AGAGACTGAG CAACAGTGTC TTTCTCTGAA
AAAGGAAAAT 360
ATAAAAATGA AGCAAGAGGT TGAGGATTCT GTAACAAAGA TGGGAGATGC
ACATAAGGAG 420
TTGGAACAAT CACATATAAA CTATGTGAAA GAAATTGAAA ATTTGAAAAA
TGAGTTGATG 480
GCAGTACGTT CCAAATACAG TGAAGACAAA GCTAACTTAC AAAAGCAGCT
GGAAGAACAA 540
TGAATACGCA ATTAGAACTT TCAGAACAAC TTAAATTTCA GAACAACTCT
GAAGATAATG 600
TTAAAAAACT ACAAGAAGAG ATTGAGAAAA TTAGGCCAGG CTTTGAGGAG
CAAATTTTAT 660
ATCTGCAAAA GCAATTAGAC GCTACCACTG ATGAAAAGAA GGAAACAGTT
ACTCAACTCC 720
AAAATATCAT TGAGGCTAAT TCTCAGCATT ACCAAAAAAA TATTAATAGT
TTGCAGGAAG 780
AGCTTTTACA GTTGAAAGCT ATACACCAAG AAGAGGTGAA AGAGTTGATG

TGCCAGATTG 840
AAGCATCAGC TAAGGAACAT GAAGCAGAGA TAAATAAGTT GAACGAGCTA
AAAGAGAACT 900
TAGTAAAACA ATGTGAGGCA AGTGAAAAGA ACATCCAGAA GAAATATGAA
TGTGAGTTAG 960
AAAATTTAAG GAAAGCCACC TCAAATGCAA ACCAAGACAA TCAGATATGT
TCTATTCTCT 1020
TGCAAGAAAA TACATTTGTA GAACAAGTAG TAAATGAAAA AGTCAAACAC
TTAGAAGATA 1080
CCTTAAAAGA ACTTGAATCT CAACACAGTA TCTTAAAAGA TGAGGTAACT
TATATGAATA 1140
ATCTTAAGTT AAAACTTGAA ATGGATGCTC AACATATAAA GGATGAGTTT
TTTCATGAAC 1200
GGGAAGACTT AGAGTTTAAA ATTAATGAAT TATTACTAGC TAAAGAAGAA
CAGGGCTGTG 1260
TAATTGAAAA ATTAAAATCT GAGCTAGCAG GTTTAAATAA ACAGTTTTGC
TATACTGTAG 1320
AACAGCATAA CAGAGAAGTA CAGAGTCTTA AGGAACAACA TCAAAAAGAA
ATATCAGAAC 1380
TAAATGAGAC ATTTTTGTCA GATTCAGAAA AAGAAAAATT AACATTAATG
TTTGAAATAC 1440
AGGGTCTTAA GGAACAGTGT GAAAACCTAC AGCAAGAAAA GCAAGAAGCA
ATTTTAAATT 1500
ATGAGAGTTT ACGAGAGATT ATGGAAATTT TACAAACAGA ACTGGGGGAA
TCTGCTGGAA 1560
AAATAAGTCA AGAGTTCGAA TCAATGAAGC AACAGCAAGC ATCTGATGTT
CATGAACTGC 1620
AGCAGAAGCT CAGAACTGCT TTTACTGAAA AAGATGCCCT TCTCGAAACT
GTGAATCGCC 1680
TCCAGGGAGA AAATGAAAAG TTACTATCTC AACAAGAATT GGTACCAGAA
CTTGAAAATA 1740
CCATAAAGAA CCTTCAAGAA AAGAATGGAG TATACTTACT TAGTCTCAGT
CAAAGAGATA 1800
CCATGTTAAA AGAATTAGAA GGAAAGATAA ATTCTCTTAC TGAGGAAAAA
GATGATTTTA 1860
TAAATAAACT GAAAAATTCC CATGAAGAAA TGGATAATTT CCATAAGAAA
TGTGAAAGGG 1920
AAGAAAGATT GATTCTTGAA CTTGGGAAGA AAGTAGAGCA AACTATCCAG
TACAACAGTG 1980
AACTAGAACA AAAGGT
1996

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 3642 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

GTCCTGCTGA AGCTCACTCA GATTCCCTCA TTGATACCTT TCCTGAGTGT
AGTACGGAAG 60
GCTTCTCCAG TGACAGTGAT CTGGTATCTC TTACTGTTGA TGTGGATTCT
CTTGCTGAGT 120
TAGATGATGG AATGGCTTCC AATCAAAATT CTCCCATTAG AACTTTTGGT
CTCAATCTTT 180
CTTCGGATTC TTCAGCACTA GGGGCTGTTG CTTCTGACAG TGAACAGAGC
AAAACAGAAG 240
AAGAACGGGA AAGTCGTAGC CTCTTTCCTG GCAGTTTAAA GCCGAAGCTT
GGCAAGAGAG 300
ATTATTTGGA GAAAGCAGGA GAATTAATAA AGCTGGCTTT AAAAAAGGAA
GAAGAAGACG 360
ACTATGAAGC TGCTTCTGAT TTTTATAGGA AGGGAGTTGA TTTACTCCTA
GAAGGTGTTC 420
AAGGAGAGTC AAGCCCTACC CGTCGAGAAG CTGTGAAGAG AAGAACAGCC
GAGTACCTCA 480
TGCGGGCAGA AAGTATCTCT AGTCTTTATG GGAAACCTCA GCTTGATGAT
GTATCTCAGC 540
CTCCAGGATC ACTAAGTTCA AGGCCCCTTT GGAACCTAAG GAGCCCTGCC
GAGGAGCTGA 600
AGGCCTTCAG AGTCCTTGGG GTGATTGACA AGGTTTTACT TGTAATGGAC
ACAAGGACAG 660
AACACACTTT CATTTTAANA GGTCTAAGGA AAAGCAGTGA ATACAGCAGG
AACAGAAAGA 720
CCATCCNCCC CCGCTGTGTG CCCANCATGG TGTGTCTGCA TAAGTACATC
ATCTCTGAAG 780
AGTCANTATT TCTTGTGCTG CAGCATGCGG AANGTGGCAA ACTGTGGTCA
TATATCAGTA 840
AATTTCTAAA CAGAAGTCCT GAAGAAAGCT TTGACATCAA GGAAGTGAAA
AAACCTACAC 900
TTGCAAAAGT TCACCTGCAG CAGCCAACTT CTAGTCCTCA GGACAGCAGT
AGCTTTGAAT 960
CCAGAGGAAG TGATGGTGGA AGCATGCTTA AAGCTCTGCC TTTGAAGAGT
AGTCTTACTC 1020
CAAGTTCTCA AGATGACAGC AACCAGGAAG ATGATGGCCA AGATAGCTCT
CCAAAGTGGC 1080
CAGATTCTGG TTCAAGTTCA GAAGAAGAAT GTACTACTAG TTATTTAACA
TTATGCAATG 1140

AATATGGGCA AGAAAAGATT GAACCAGGGT CTTTGAATGA GGAGCCCTTC
ATGAAGACTG 1200
AAGGGAATGG TGTTGATACA AAAGCTATTA AAAGCTTCCC AGCACACCTT
GCTGCTGACA 1260
GTGACAGCCC CAGCACACAG CTGAGAGCTC ACGAGCTGAA GTTCTTCCCC
AACGATGACC 1320
CAGAAGCAGT TAGTTCTCCA AGAACATCAG ATTCCCTCAG TAGATCAAAA
AATAGCCCCA 1380
TGGAATTCTT TAGGATAGAC AGTAAGGATA GCGCAAGTGA ACTCCTGGGA
CTTGACTTTG 1440
GAGAAAAATT GTATAGTCTA AAATCAGAAC CTTTGAAACC ATTCTTTACT
CTTCCAGATG 1500
GAGACAGTGC TTCTAGGAGT TTTAATACTA GTGAAAGCAA GGTAGAGTTT
AAAGCTCAGG 1560
ACACCATTAG CAGGGGCTCA GATGACTCAG TGCCAGTTAT TTCATTTAAA
GATGCTGCTT 1620
TTGATGATGT CAGTGGTACT GATGAAGGAA GACCTGATCT TCTTGTAAAT
TTACCTGGTG 1680
AATTGGAGTC AACAAGAGAA GCTGCAGCAA TGGGACCTAC TAAGTTTACA
CAAACTAATA 1740
TAGGGATAAT AGAAAATAAA CTCTTGGAAG CCCCTGATGT TTTATGCCTC
AGGCTTAGTA 1800
CTGAACAATG CCAAGCACAT GAGGAGAAAG GCATAGAGGA ACTGAGTGAT
CCCTCTGGGC 1860
CCAAATCCTA TAGTATAACA GAGAAACACT ATGCACAGGA GGATCCCAGG
ATGTTATTTG 1920
TAGCANCTGT TGATCATAGT AGTTCAGGAG ATATGTCTTT GTTACCCAGC
TCAGATCCTA 1980
AGTTTCAAGG ACTTGGAGTG GTTGAGTCAN CAGTAACTGC AAACAACACA
GAAGAAAGCT 2040
TATTCCGTAT TTGTAGTCCA CTCTCAGGTG CTAATGAATA TATTGCAAGC
ACAGACACTT 2100
TAAAAACAGA AGAAGTATTG CTGTTTACAG ATCAGACTGA TGATTTGGCT
AAAGAGGAAC 2160
CAACTTCTTT ATTCCANAGA GACTCTGAGA CTAAGGGTGA AAGTGGTTTA
GTGCTAGAAG 2220
GAGACAAGGA AATACATCAG ATTTTTGAAG GACCTTGATA AAAAATTAGC
ACTANCCTCC 2280
AGGTTTTACA TCCCAGAGGG CTGCATTCAA AGNTGGGCAG CTGAAATGGT
GGTAGCCCTT 2340
NGATGCTTTA ACATAGAGAG GGAATTGTGT GCCGCGATTG AACCCAAACA
ANATNTTATT 2400
GAATGATAGA GGACACATTC AGNTAACGTA TTTTAGCAGG TGGAGTGAGG
TTGAAGATTC 2460
CTGTGACAGC GATGCCATAG AGAGAATGTA CTGTGCCCCA GAGGTTGGAG

CAATCACTGA 2520
AGAAACTGAA GCCTGTGATT GGTGGAGTTT GGGTGCTGTC CTCTTTGAAC
TTNTCACTGG 2580
CAAGACTCTG GTTGAATGCC ATCCAGCAGG AATAAATACT CACACTACTT
TGAACATGCC 2640
AGAATGTGTC TCTGAAGAGG CTCGCTCACT CATTCAACAG CTCTTGCAGT
TCAATCCTCT 2700
GGAACGACTT GGTGCTGGAG TTGCTGGTGT TGAAGATATC AAATCTCATC
CATTTTTTAC 2760
CCCTGTGGAT TGGGCAGAAC TGATGAGATG AACGTAATGC AGGGTTATCT
TCACACATTC 2820
TGATCTTCTC TGTGACAGGC ATCTCCAGCA CTGAGGCACC TCTGACTCAC
AGTTACTTAT 2880
GGAGCACCAA AGCATTTGGA TAAGGACCGT TATAGGAAAT GGGGGGGAAA
TGGCTAAAAG 2940
AGAACAATTT GTTTACAATT ACAAGATATT AGCTAATTGT GCCAGGGGCT
GTTATATACA 3000
TATATACACA ACCAAGGTGT GATCTGAATT TAATCCACAT TTGGTGTTGC
AGATGAGTTG 3060
TAAAGCCAAC TGAAAGAGTT CCTTCAAGAA GTTCCTCTGA TAGGAAGCTA
GAAGTGTAGA 3120
ATGAAGTTTT ACTTGACAGA AGGACCTTTA CATGGCAGCT AACAGTGCTT
TTTGCTGACC 3180
AGGATTGGTT TATATGATTA AATTAATATT TGCTTAATAA TACACTAAAA
GTATATGAAC 3240
AATGTCATCA ATGAAACTTA AAAGCGAGAA AAAAGAATAT ACACATAATT
TCTGACGGAA 3300
AACCTGTACC CTGATGCTGT ATAATGTATG TTGAATGTGG TCCCAGATTA
TTTCTGTAAG 3360
AAGACACTCC ATGTTGTCAG CTTTGTACTC TTTGTTGATA CTGCTTATTT
AGAGAAGGGT 3420
TCATATAAAC ACTCACTCTG TGTCTTCAAC AGCATCTTTC TTTCCCCATC
TTTCTATTTT 3480
CTGCACCCTC TGCTTGTTCC CTCATATTCT GTTCTTCCGA CTCCTGCTAA
CACACATGCA 3540
ACAAAAAAGG GAAGGGAGTG CTTATTTCCC TTTGTGTAAG GACTAAGAAA
TCATGATATC 3600
AAATAAACAT GGTGAAACAT TNANAAAAAA AAAAAAAAAA AA
3642

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1397 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

GTTCAACTCA ATAGAAGATG ACGTTTGCCA GCTAGTGTAT GTGGAAAGAG
CTGAAGTGCT 60
CAAATCTGAA GATGGCGCCA GCCTCCCAGT GATGGACCTG ACTGAACTCC
CCAAGTGCAC 120
GGTGTGTCTG GAGCGCATGG ACGAGTCTGT GAATGGCATC CTCACAACGT
TATGTAACCA 180
CATCTTCCAC AGCCAGTGTC TACAGCGCTG GGACGATACC ACGTGTCCTG
TTTGCCGGTA 240
CTGTCAAACG CCCGAGCCAG TAGAAGAAAA TAAGTGTTTT GAGTGTGGTG
TTCAGGAAAA 300
TCTTTGGATT TGTTTAATAT GCGGCCACAT AGGATGTGGA CGGTATGTCA
GTCGACATGC 360
TTATAAGCAC TTTGAGGAAA CGCAGCACAC GTATGCCATG CAGCTTACCA
ACCATCGAGT 420
CTGGGACTAT GCTGGAGATA ACTATGTTCA TCGACTGGTT GCAAGTAAAA
CAGATGGAAA 480
AATAGTACAG TATGAATGTG AGGGGGATAC TTGCCAGGAA GAGAAAATAG
ATGCCTTACA 540
GTTAGAGTAT TCATATTTAC TAACAAGCCA GCTGGAATCT CAGCGAATCT
ACTGGGAAAA 600
CAAGATAGTT CGGATAGAGA AGGACACAGC AGAGGAAATT AACAACATGA
AGACCAAGTT 660
TAAAGAAACA ATTGAGAAGT GTGATAATCT AGAGCACAAA CTAAATGATC
TCCTAAAAGA 720
AAAGCAGTCT GTGGAAAGAA AGTGCACTCA GCTAAACACA AAAGTGGCCA
AACTCACCAA 780
CGAGCTCAAA GAGGAGCAGG AAATGAACAA GTGTTTGCGA GCCAACCAAG
TCCTCCTGCA 840
GAACAAGCTA AAAGAGGAGG AGAGGGTGCT GAAGGAGACC TGTGACCAAA
AAGATCTGCA 900
GATCACCGAG ATCCAGGAGC AGCTGCGTGA CGTCATGTTC TACCTGGAGA
CACAGCAGAA 960
AGATCAACCA TCTGCCTGCC GAGACCCGGC AGGAAATCCA GGAGGGACAG
ATCAACATCG 1020
CCATGGCCTC GGCCTCGAGC CCTGCCTCTT CGGGGGGCAG TGGGAAGTTG
CCCTCCAGGA 1080
AGGGCCGCAG CAAGAGGGGC AAGTGACCTT CAGAGCAACA GACATCCCTG
AGACTGTTCT 1140
CCCTGACACT GTGAGAGTGT GCTGGGACCT TCAGCTAAAT GTGAGGGTGG
GCCCTAATAA 1200

GTACAAGTGA GGATCAAGCC ACAGTTGTTT GGCTCTTTCA TTTGCTAGTG
TGTGATGTAG 1260
TGAATGTAAA GGGTGCTGAC TGGAGAGCTG ATAGAAAGGC GCTGCGTTCG
AAAAGGTCTT 1320
AAGAGTTCAC TAACCTCACA TTCTAATGAC CANTTTGCCT TCCTGCTTGG
TAGAAGCCCC 1380
ACACTCTGCT GTGCATT
1397

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 800 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

CGGTAATTGA GCANACTTAA AATAAGACCT GTGTTGGAAT TTAGTTTCCT
CTGAAGAGGT 60
AGAGGGATAG GTTAGTAAGA TGTATTGTTA AACAACAGGT TTTAGTTTTT
GCTTTTATAA 120
TTAGCCACAG GTTTTCAAAT GATCACATTT CAGAATAGGT TTTTAGCCTG
TAATTAGGCC 180
TCATCCCCTT TGACCTAAAT GTCTTACATG TTACTTGTTA GCACATCAAC
TGTATCACTA 240
ATCACCATCT GNTTTTGTGG GATGTGCTGC AGCATTTCCC AAAAAACTTT
ACGTGTAATG 300
TTGCAAAATG AATGTACTCA GACATTCTTA ATTTTTACTT AGGGCAGACC
AACTCTTTGA 360
GTCTCTCTTG GACTTATATA TACAGATATC TTAAGAGTGG GAATGTAAAG
CATAACCTAA 420
TTCTCTTTCC TATAGAGATT CTATTTTATT TAAAATCTAT TTTTACACTA
GTTAGAATCC 480
TGCTGTTTTG GCCAAGTACT TGTCTTGCAT GTCTGACCTT GCAGAAGCTG
GGGTGGATCA 540
TAGCATACTA ATGAAGAGAA TTAGAAGTAG TTTACAAAGC TCGCTCACTC
CTCATTTCTC 600
TGTGATCCCT TCTATCCAGT GGCCCCACCA CCACCTGGGA AAACAGATTT
TTCAGTACAG 660
GTGGGATAAA TGCTCTGAAA GGCTGTGCCC AGAGGAATGA GCAAATAGGC
AAGTGTTTCC 720
AAACTACTTG GAGGTTTACA AAAAATATGT CCCAGAAAAA AAAAAAATCT
TACCAAGATA 780

CGTAAAAAAA AAAAAAAAAA
800

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1810 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GCAGCTCCCA GGTGCGTGTT AAAAGCTGGA GGGGGGATAT GTGATCCCAG
GACCAAAAGC 60
GCGGGGCCAG ACTCATCGGT TCATTCAACA ACCAGTATTT AGTGCCTGCT
GTGTTCTGCA 120
GGCCCTGCCA TAGGCGCTTG ATACAGCGGT GCATAGCGTA TGAAAAAGAT
CTGTCCTGGC 180
TGAGCATCCG TAATATAAAA ATCTGAAATC TGAAATGCTC CAAAATCCTA
AACTTTTTGA 240
GTGCTGACAT TATGCCACAA ATGGAAAATT TCATACCTGA CCTTATGTGG
GTTGCANTCA 300
AAACACAGGT GCACAACACC CAGTTCATGC AACATCCCCA ATGGGAAAAA
AGACCCCCCC 360
AGCTCTCTTC TGCTGCAGTT TTTCTGCTCA CACCTGGATT TCCCCATGCA
TTCCCACAAA 420
AAGTAATTAA ATGGCATGCG TGCAGGCTGG ACACGCCAAC AACAGGTTTC
CCACAATGCC 480
CCACATGGGG CCAAGACCTG TGTGCATTAC TCATTGCATT TTTTTGCTTA
TTCTCTGCTG 540
TGTGGTATAA ATATATTGTT GAAAATGTCA AAAAGACCTA AAGATACCCC
TGTGAATATC 600
AGTGATAAGA AAAAGAGGAA GCATTTATGT TTATCTATAG CACAGAAAGT
CAAGTTGTTG 660
GAGAAACTGG ACAGTGGTGT AAGTGTGAAA CATCTTACAG AAGAGTATGG
TGTTGGAATG 720
ACCACCATAT ATGACCTGAA GAAACAGAAG GATAAACTGT TGAAGTTTTA
TGCTGAAAGT 780
GATGAGCAGA TATTAATGAA AAATAGAAAA ACACTTCATA AAGCTAAAAA
TGAAGATCTT 840
GATCGTGTAT TGAAAGAGTG GATCCGTCAG CGTCGCAGTG AACACATGCC
ACTTAATGGT 900
ATGCTGATCA TGAAACAAGC AAAGATATAT CACAATGAAC TAAAAATTGA
GGGGAACTGT 960

GAATATTCAA CAGGCTGGTT GCAGAAATTT AAGAAAAGAC ATGGCATTAA
ATTTTTAAAG 1020
ACTTGTGGCA ATAAAGCATC TGCTGGTCAT GAAGCAACAG AGAAGTTTAC
TGGCAATTTC 1080
AGTAATGATG ATGAACAAGA TGGTAACTTT GAAGGATTCA NTATGTCAAG
TGAGAAAAAA 1140
ATAATGTCTG ACCTCCTTAC ATATACAAAA AATATACATC CAGAGACTGT
CAGTAAGCTG 1200
GAAGAAGAGG ATATCTTTNA TGTTTTTAAC AGTAATAATG AGGCTCCAGT
TGTTCATTCA 1260
TTGTCCAATG GTGAAGTAAC AAAAATGGTT CTGAATCAAG ATGATCATGA
TGATAATGAT 1320
AATGAAGATG ATGTTAACAC TGCAGAAAAA GTGCCTATAG ACGACATGGT
AAAAATGTGT 1380
GATGGGCTTA TTAAAGGACT AGAGCAGCAT GCATTCATAA CAGAGCAAGA
AATCATGTCA 1440
GTTTATAAAA TCAAAGAGAG ACTTCTAAGA CAAAAAGCAT CATTAATGAG
GCAGATGACT 1500
CTGAAAGAAA CATTTAAAAA AGCCATCCAG AGGAATGCTT CTTCCTCTCT
ACAGGACCCA 1560
CTTCTTGGTC CCTCAACTGC TTCTGATGCT TCTTCTCACC TAAAAATAAA
ATAAAATACA 1620
GTGTACAGTA ACCTTTTAGT CAAAACAGCA TCATACTTGG AAACTGAAAG
CCTACTGTTA 1680
TTTGTTATTG TTGCTTAACA GCTGATACAG GTATTCTGGT GACACTACTG
TGCTGGCTTA 1740
CTTAACCTGA ATACACTATT TTTTTCGTTG TAAAAAAAAA AAAAAAANAA
NAAAAAAAAA 1800
AAAAAANANA
1810

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 70 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Ala Arg Glu Gly Gly Lys Met Val Leu Glu Ser Thr Met Val
Cys Val
1 5 10
15

Asp Asn Ser Glu Tyr Met Arg Asn Gly Asp Phe Leu Pro Thr Arg Leu
20 25 30
Gln Ala Gln Gln Asp Ala Val Asn Ile Xaa Cys His Ser Lys Thr Arg
35 40 45
Ser Asn Pro Glu Asn Asn Val Gly Leu Ile Thr Leu Ala Asn Asp Cys
50 55 60
Glu Val Leu Thr Thr Leu
65 70

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 100 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Ala Arg Glu Ser Thr Met Val Cys Val Asp Asn Ser Glu Tyr Met Arg
1 5 10 15
Asn Gly Asp Phe Leu Pro Thr Arg Leu Gln Ala Gln Gln Asp Ala Val
20 25 30
Asn Ile Val Cys His Ser Lys Thr Arg Ser Asn Pro Glu Asn Asn Val
35 40 45
Gly Leu Ile Thr Leu Ala Asn Asp Cys Glu Val Leu Thr Thr Leu Thr
50 55 60
Pro Asp Thr Gly Arg Ile Leu Ser Lys Leu His Thr Val Gln Pro Lys
65 70 75 80
Gly Lys Ile Thr Phe Cys Thr Gly Ile Arg Val Ala His Leu Ala Leu
85 90 95
Lys His Arg Gln
100

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 214 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

CGGCACGAGA AGGTGGCAAG ATGGTGTTGG AAAGCACTAT GGTGTGTGTG
GACAACAGTG 60
AGTATATGCG GAATGGAGAC TTCTTACCCA CCAGGCTGCA GGCCCAGCAG
GATGCTGTCA 120
ACATANTTTG TCATTCAAAG ACCCGCAGCA ACCCTGAGAA CAACGTGGGC
CTTATCACAC 180
TGGCTAATGA CTGTGAAGTG CTGACCACAC TCAC
214

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 375 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

TATGGACACA TTTGAGCCAG CCAAGGAGGA GGATGATTAC GACGTGATGC
AGGACCCCGA 60
GTTCCTTCAG AGTGTCCTAG AGAACCTCCC AGGTGTGGAT CCCAACAATG
AAGCCATTCG 120
AAATGNTATG GGCTCCCTGG CCTCCCAGGC CACCAAGGAC GGCAAGAAGG
ACAAGAAGGA 180
GGAAGACAAG AAGTGAGACT GGAGGGAAAG GGTAGCTGAG TCTGCTTAGG
GGACTGCATG 240
GGAAGCACGG AATATAGGGT TAGATGTGTG TTATCTGTAA CCATTACAGC
CTAAATAAAG 300
CTTGGCAACT TTTTAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA
AAAAAAAAAA 360
AAAAAAAAAC TCGAG
375

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 304 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

CGGCACGAGA AAGCACTATG GTGTGTGTGG ACAACAGTGA GTATATGCGG
AATGGAGACT 60
TCTTACCCAC CAGGCTGCAG GCCCAGCAGG ATGCTGTCAA CATAGTTTGT
CATTCAAAGA 120
CCCGCAGCAA CCCTGAGAAC AACGTGGGCC TTATCACACT GGCTAATGAC
TGTGAAGTGC 180
TGACCACACT CACCCCAGAC ACTGGCCGTA TCCTGTCCAA GCTACATACT
GTCCAACCCA 240
AGGGCAAGAT CACCTTCTGC ACGGGCATCC GCGTTGCCCA TCTGGCTCTG
AAGCACCGAC 300
AAGG
304

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Val Arg Gly Gly Gly Gly Gly Gly Pro Gly Gly Gly Gly Val
Gly Gly
1 5 10
15
Arg Cys Gly Gly Gly Gly
20

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 78 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

```
Ala Arg Ala Ala Arg Ala Lys Ala Gln Ala Leu Ile Gln Asn
Leu Ser
1               5                   10
15
Leu Leu Leu Val Asp Ala Ser Val Gly Thr Ile Gln Cys Leu
Glu Glu
            20                  25                  30
Ile Leu Cys Glu Phe Val Gln Lys Asp Glu Leu Lys Pro Ala
Val Thr
        35                  40                  45
Xaa Leu Leu Trp Glu Arg Ala Thr Glu Lys Val Ala Cys Cys
Pro Leu
    50                  55                  60
Glu Arg Cys Ser Ser Val Met Leu Leu Gly Met Met Ala Arg
65                  70                  75
```

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 384 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

```
Lys Met Val Leu Glu Ser Thr Met Val Cys Val Asp Asn Ser
Glu Tyr
1               5                   10
15
Met Arg Asn Gly Asp Phe Leu Pro Thr Arg Leu Gln Ala Gln
Gln Asp
            20                  25                  30
Ala Val Asn Ile Val Cys His Ser Lys Thr Arg Ser Asn Pro
Glu Asn
        35                  40                  45
Asn Val Gly Leu Ile Thr Leu Ala Asn Asp Cys Glu Val Leu
Thr Thr
    50                  55                  60
Leu Thr Pro Asp Thr Gly Arg Ile Leu Ser Lys Leu His Thr
```

Val Gln
65 70 75
80
Pro Lys Gly Lys Ile Thr Phe Cys Thr Gly Ile Arg Val Ala
His Leu
85 90
95
Ala Leu Lys His Arg Gln Gly Lys Asn His Lys Met Arg Ile
Ile Ala
100 105 110
Phe Val Gly Ser Pro Val Glu Asp Asn Glu Lys Asp Leu Val
Lys Leu
115 120 125
Ala Lys Arg Leu Lys Lys Glu Lys Val Asn Val Asp Ile Ile
Asn Phe
130 135 140
Gly Glu Glu Glu Val Asn Thr Glu Lys Leu Thr Ala Phe Val
Asn Thr
145 150 155
160
Leu Asn Gly Lys Asp Gly Thr Gly Ser His Leu Val Thr Val
Pro Pro
165 170
175
Gly Pro Ser Leu Ala Asp Ala Leu Ile Ser Ser Pro Ile Leu
Ala Gly
180 185 190
Glu Gly Gly Ala Met Leu Gly Leu Gly Ala Ser Asp Phe Glu
Phe Gly
195 200 205
Val Asp Pro Ser Ala Asp Pro Glu Leu Ala Leu Ala Leu Arg
Val Ser
210 215 220
Met Glu Glu Gln Arg Gln Arg Gln Glu Glu Glu Ala Arg Arg
Ala Ala
225 230 235
240
Ala Ala Ser Ala Ala Glu Ala Gly Ile Ala Thr Thr Gly Thr
Glu Asp
245 250
255
Ser Asp Asp Ala Leu Leu Lys Met Thr Ile Ser Gln Gln Glu
Phe Gly
260 265 270
Arg Thr Gly Leu Pro Asp Leu Ser Ser Met Thr Glu Glu Glu

```
Gln Ile
             275                 280                 285
     Ala Tyr Ala Met Gln Met Ser Leu Gln Gly Ala Glu Phe Gly
Gln Ala
         290                 295                 300
     Glu Ser Ala Asp Ile Asp Ala Ser Ser Ala Met Asp Thr Ser
Glu Pro
     305                 310                 315
320
     Ala Lys Glu Glu Asp Asp Tyr Asp Val Met Gln Asp Pro Glu
Phe Leu
                    325                 330
335
     Gln Ser Val Leu Glu Asn Leu Pro Gly Val Asp Pro Asn Asn
Glu Ala
                340                 345                 350
     Ile Arg Asn Ala Met Gly Ser Leu Pro Pro Arg Pro Pro Arg
Thr Ala
             355                 360                 365
     Arg Arg Thr Arg Arg Arg Lys Thr Arg Ser Glu Thr Gly Gly
Lys Gly
         370                 375                 380
```

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 68 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```
     Ala Arg Asp Ala Tyr Ser Phe Ser Arg Lys Ile Thr Glu Ala
Ile Gly
     1               5                   10
15
     Ile Ile Ser Lys Met Met Tyr Glu Asn Thr Thr Thr Val Val
Gln Glu
                20                  25                  30
     Val Ile Glu Phe Phe Val Met Val Phe Gln Phe Gly Val Pro
Gln Ala
             35                  40                  45
     Leu Phe Gly Val Arg Arg Met Leu Pro Leu Ile Trp Ser Lys
Glu Pro
```

50 55 60
Gly Val Arg Glu
65

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 97 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Ala Arg Ala Gln Ala Leu Phe Gly Val Arg Arg Met Leu Pro Leu Ile
1 5 10 15
Trp Ser Lys Glu Pro Gly Val Arg Glu Ala Val Leu Asn Ala Tyr Arg
20 25 30
Gln Leu Tyr Leu Asn Pro Lys Gly Asp Ser Ala Arg Ala Lys Ala Gln
35 40 45
Ala Leu Ile Gln Asn Leu Ser Leu Leu Leu Val Asp Ala Ser Val Gly
50 55 60
Thr Ile Gln Cys Leu Glu Glu Ile Leu Cys Glu Phe Val Gln Lys Asp
65 70 75 80
Glu Leu Lys Pro Ala Val Thr Gln Leu Leu Trp Glu Pro Ala Thr Glu
85 90 95
Lys

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 116 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Ala Arg Ala Thr Thr Ala Phe Gly Cys Arg Ile Trp Asn Pro Cys Ala
1 5 10 15
Ala Leu Thr Met Lys Gln Ser Ser Asn Val Pro Ala Phe Leu Ser Lys
20 25 30
Leu Trp Thr Leu Val Glu Glu Thr His Thr Asn Glu Phe Ile Thr Trp
35 40 45
Ser Gln Asn Gly Gln Ser Phe Leu Val Leu Asp Glu Gln Arg Phe Ala
50 55 60
Lys Glu Ile Leu Pro Lys Tyr Phe Lys His Asn Asn Met Ala Ser Phe
65 70 75 80
Val Arg Gln Leu Asn Met Tyr Gly Phe Arg Lys Val Ile His Ile Asp
85 90 95
Ser Gly Ile Val Lys Gln Glu Arg Asp Gly Pro Val Glu Phe Gln His
100 105 110
Pro Tyr Phe Gln
115

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 124 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

Ala Arg Gly Ala Thr Cys Glu Arg Cys Lys Gly Gly Phe Ala Pro Ala
1 5 10 15
Glu Lys Ile Val Asn Ser Asn Gly Glu Leu Tyr His Glu Gln Cys Phe

```
                20                  25                  30
     Val Cys Ala Gln Cys Phe Gln Gln Phe Pro Glu Gly Leu Phe
Tyr Glu
            35                  40                  45
     Phe Glu Gly Arg Lys Tyr Cys Glu His Asp Phe Gln Met Leu
Phe Ala
        50                  55                  60
     Pro Cys Cys His Gln Cys Gly Glu Phe Ile Ile Gly Arg Val
Ile Lys
     65                  70                  75
80
     Ala Met Asn Asn Ser Trp His Pro Glu Cys Phe Arg Cys Asp
Leu Cys
                    85                  90
95
     Gln Glu Val Leu Ala Asp Ile Gly Phe Val Lys Asn Ala Gly
Arg His
                100                 105                 110
     Leu Cys Arg Pro Cys His Asn Arg Glu Lys Ala Arg
            115                 120
```

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 768 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

```
TACGAGGAGG AGGAGGAGGA GGCCCCGGAG GAGGAGGCGT TGGAGGTCGA
TGCGGAGGCG      60
GAGGATGAGG AGGCCGAGGC GCCGGAGGAG GCCGAGGCGC CGGAGCAGGA
GGAGGCCGGC     120
CGGAGGCGGC ATGAGACGAG CGTGGCGGCC GCGGCTGCTC GGGGCCGCGC
TGGTTGCCCA     180
TTGACAGCGG CGTCTGCAGC TCGCTTCAAG ATGGCCGCTT GGCTCGCATT
CATTTTCTGC     240
TGAACGACTT TTAACTTTCA TTGTCTTTTC CGCCCGCTTC GATCGCCTCG
CGCCGGCTGC     300
TCTTTCCGGG ATTTTTTATC AAGCAGAAAT GCATCGAACA ACGAGAATCA
AGATCACTGA     360
GCTAAATCCC CACCTGATGT GTGTGCTTTG TGGAGGGTAC TTCATTGATG
CCACAACCAT     420
```

AATAGAATGT CTACATTCCT TCTGTAAAAC GTGTATTGTT CGTTACCTGG
AGACCAGCAA 480
GTATTGTCCT ATTTGTGATG TCCAAGTTCA CAAGACCAGA CCACTACTGA
ATATAAGGTC 540
AGATAAAACT CTCCAAGATA TTGTATACAA ATTAGTTCCA GGGCTTTTCA
AAAATGAAAT 600
GAAGAGAAGA AGGGATTTTT ATGCAGCTCA TCCTTCTGCT GATGCTGCCA
ATGGCTCTAA 660
TGAAGATNGA GGAGAGGTTG CAGATGAAGA TAAGAGAATT ATAACTGATG
ATGAGATAAT 720
AAGCTTATCC ATTGAATTCT TTGACCAGAA CAGATTGGAT CGGAAAGT
768

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 642 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

TTTAAATAAA CCAGCAGGTT GCTAAAAGAA GGCATTTTAT CTAAAGTTAT
TTTAATAGGT 60
GGTATAGCAG TAATTTTAAA TTTAAGAGTT GCTTTTACAG TTAACAATGG
AATATGCCTT 120
CTCTGCTATG TCTGAAAATA GAAGNTATTT ATTATGAGCT TNTACAGGTA
TTTTTAAATA 180
GAGCAAGCAT GTTGAATTTA AAATATGAAT AACCCCACCC AACAATTTTC
AGTTTATTTT 240
TTGCTTTGGT CGAACTTGGT GTGTGTTCAT CACCCATCAG TTATTTGTGA
GGGTGTTTAT 300
TCTATATGAA TATTGTTTCA TGTTTGTATG GGAAAATTGT AGCTAAACAT
TTCATTGTCC 360
CCAGTCTGCA AAAGAAGCAC AATTCTATTG CTTTGTCTTG CTTATAGTCA
TTAAATCATT 420
ACTTTTACAT ATATTGCTGT TACTTCTGCT TTCTTTAAAA ATATAGTAAA
GGATGTTTTA 480
TGAAGTCACA AGATACATAT ATTTTTATTT TGACCTAAAT TTGTACAGTC
CCATTGTAAG 540
TGTTGTTTCT AATTATAGAT GTAAAATGAA ATTTCATTTG TAATTGGAAA
AAATCCAATA 600
AAAAGGATAT TCATTTAAAA AAAAAAAAAA AAAAAAAAAA AA
642

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 236 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

CGGCACGAGC TGCCAGAGCC AAGGCCCAGG CTTTGATTCA GAATCTCTCT
CTGCTGCTAG 60
TGGATGCCTC GGTTGGGACC ATTCAGTGTC TTGAGGAAAT TCTCTGTGAG
TTTGTGCAGA 120
AGGATGAGTT GAAACCAGCA GTGACCCANC TGCTGTGGGA GCGGGCCACC
GAGAAAGTCG 180
CCTGCTGTCC TCTGGAACGC TGTTCCTCTG TCATGCTTCT TGGCATGATG GCACGA
236

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 333 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

CCGGGCGTAT TGGCGTGCGC CTGTAATCCC AGCTAACTCA AGAGGCTGAG
GCAGGAGAAT 60
CGCCTGAACC CAGAGGCGGA GGTTGTAGTG AGCCGAAATC ACACCATTGC
ACTCCAGCTT 120
GGGCAACAAT AGCGAACCTC CATCTCAAAT TAAAAAAAAA AATGCCTACA
CGCTCTTTAA 180
AATGCAAGGC TTTCTCTTAA ATTAGCCTAA CTGAACTGCG TTGAGCTGCT
TCAACTTTGG 240
AATATATGTT TGCCAATCTC CTTGTTTTCT AATGAATAAA TGTTTTTATA
TACTTTTAGA 300
AAAAAAAAAA AAAAAAAAAA AAAAAAACTC GAG
333

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1272 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GCAAGATGGT GTTGGAAAGC ACTATGGTGT GTGTGGACAA CAGTGAGTAT
ATGCGGAATG 60
GAGACTTCTT ACCCACCAGG CTGCAGGCCC AGCAGGATGC TGTCAACATA
GTTTGTCATT 120
CAAAGACCCG CAGCAACCCT GAGAACAACG TGGGCCTTAT CACACTGGCT
AATGACTGTG 180
AAGTGCTGAC CACACTCACC CCAGACACTG GCCGTATCCT GTCCAAGCTA
CATACTGTCC 240
AACCCAAGGG CAAGATCACC TTCTGCACGG GCATCCGCGT GGCCCATCTG
GCTCTGAAGC 300
ACCGACAAGG CAAGAATCAC AAGATGCGCA TCATTGCCTT TGTGGGAAGC
CCAGTGGAGG 360
ACAATGAGAA GGATCTGGTG AAACTGGCTA AACGCCTCAA GAAGGAGAAA
GTAAATGTTG 420
ACATTATCAA TTTTGGGGAA GAGGAGGTGA ACACAGAAAA GCTGACAGCC
TTTGTAAACA 480
CGTTGAATGG CAAAGATGGA ACCGGTTCTC ATCTGGTGAC AGTGCCTCCT
GGGCCCAGTT 540
TGGCTGATGC TCTCATCAGT TCTCCGATTT TGGCTGGTGA AGGTGGTGCC
ATGCTGGGTC 600
TTGGTGCCAG TGACTTTGAA TTTGGAGTAG ATCCCAGTGC TGATCCTGAG
CTGGCCTTGG 660
CCCTTCGTGT ATCTATGGAA GAGCAGCGGC AGCGGCAGGA GGAGGAGGCC
CGGCGGGCAG 720
CTGCAGCTTC TGCTGCTGAG GCCGGGATTG CTACGACTGG GACTGAAGAC
TCAGACGATG 780
CCCTGCTGAA GATGACCATC AGCCAGCAAG AGTTTGGCCG CACTGGGCTT
CCTGACCTAA 840
GCAGTATGAC TGAGGAAGAG CAGATTGCTT ATGCCATGCA GATGTCCCTG
CAGGGAGCAG 900
AGTTTGGCCA GGCGGAATCA GCAGACATTG ATGCCAGCTC AGCTATGGAC
ACATCTGAGC 960
CAGCCAAGGA GGAGGATGAT TACGACGTGA TGCAGGACCC CGAGTTCCTT
CAGAGTGTCC 1020
TAGAGAACCT CCCAGGTGTG GATCCCAACA ATGAAGCCAT TCGAAATGCT
ATGGGCTCCC 1080
TGCCTCCCAG GCCACCAAGG ACGGCAAGAA GGACAAGAAG GAGGAAGACA

AGAAGTGAGA 1140
CTGGAGGGAA AGGGTAGCTG AGTCTGCTTA GGGGACTGCA TGGGAAGCAC
GGAATATAGG 1200
GTTAGATGTG TGTTATCTGT AACCATTACA GCCTAAATAA AGCTTGGCAA
CTTTTAAAAA 1260
AAAAAAAAAA AA
1272

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 206 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

CGGCACGAGA TGCCTACAGC TTCTCCCGGA AGATTACAGA GGCCATTGGC
ATCATCAGCA 60
AGATGATGTA TGAAAACACA ACTACAGTGG TGCAGGAGGT GATTGAATTC
TTTGTGATGG 120
TCTTCCAATT TGGGGTACCC CAGGCCCTGT TTGGGGTGCG CCGTATGCTG
CCTCTCATCT 180
GGTCTAAGGA GCCTGGTGTC CGGGAA
206

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 341 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

TACTAAAAAT AAAAAATTAG CCGGGCGTAT TGGCGTGCGC CTGTAATCCC
AGCTACTCAA 60
GAGGCTGAGG CAGGAGAATC GCCTGAACCC AGAGGCGGAG GTTGTAGTGA
GCCGAAATCA 120
CACCATTGCA CTCCAGCTTG GGCAACAATA GCGAACCTCC ATCTCAAATT
AAAAAAAAAA 180
TGCCTACACG CTCTTTAAAA TGCAAGGCTT TCTCTTAAAT TAGCCTAACT
GAACTGCGTT 240

GAGCTGCTTC AACTTTGGAA TATATGTTTG CCAATCTCCT TGTTTTCTAA
TGAATAAATG 300
TTTTTATATA CTTTTAANGA GAGAAAAAAA ANAAACTCGA G
341

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 293 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

CGGCACGAGC CCAGGCCCTG TTTGGGGTGC GCCGTATGCT GCCTCTCATC
TGGTCTAAGG 60
AGCCTGGTGT CCGGGAAGCC GTGCTTAATG CCTACCGCCA ACTCTACCTC
AACCCCAAAG 120
GGGACTCTGC CAGAGCCAAG GCCCAGGCTT TGATTCAGAA TCTCTCTCTG
CTGCTAGTGG 180
ATGCCTCGGT TGGGACCATT CAGTGTCTTG AGGAAATTCT CTGTGAGTTT
GTGCAGAAGG 240
ATGAGTTGAA ACCAGCAGTG ACCCAGCTGC TGTGGGAACC GGCCACCGAG AAA
293

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 350 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

CGGCACGAGC TACCACCGCG TTCGGGTGTA GAATTTGGAA TCCCTGCGCC
GCGTTAACAA 60
TGAAGCAGAG TTCGAACGTG CCGGCTTTCC TCAGCAAGCT GTGGACGCTT
GTGGAGGAAA 120
CCCACACTAA CGAGTTCATC ACCTGGAGCC AGAATGGCCA AAGTTTTCTG
GTCTTGGATG 180
AGCAACGATT TGCAAAAGAA ATTCTTCCCA AATATTTCAA GCACAATAAT
ATGGCAAGCT 240
TTGTGAGGCA ACTGAATATG TATGGTTTCC GTAAAGTAAT ACATATCGAC

TCTGGAATTG 300
TTAAGCAAGA AAGAGATGGT CCTGTAGAAT TTCAGCATCC TTACTTCCAA
350

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 377 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

TCCTAAAGCT TTCTCTGCTC CAGTTATTTT TATTAAATAT TTTTCACTTG
GCTTATTTTT 60
AAAACTGGGA ACATAAAGTG CCTGTATCTT GTAAAACTTC ATTTGTTTCT
TTTGGTTCAG 120
AGAAGTTCAT TTATGTTCAA AGACGTTTAT TCATGTTCAA CAGGAAAGAC
AAAGTGTACG 180
TGAATGCTCG CTGTCTGATA GGGTTCCAGC TCCATATATA TAGAAAGATC
GGGGGTGGGA 240
TGGGATGGAG TGAGCCCCAT CCAGTTAGTT GGACTAGTTT TAAATAAAGG
TTTTCCGGTT 300
TGTGTTTTTT TGAACCATAC TGTTTAGTAA AATAAATACA ATGAATGTTG
NAAAAAAAAA 360
AAAAAAAAAA ACTCGAG
377

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 374 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

CGGCACGAGG CGCCACTTGC GAGCGCTGCA AGGGCGGCTT TGCGCCCGCT
GAGAAGATCG 60
TGAACAGTAA TGGGGAGCTG TACCATGAGC AGTGTTTCGT GTGCGCTCAG
TGCTTCCAGC 120
AGTTCCCAGA AGGACTCTTC TATGAGTTTG AAGGAAGAAA GTACTGTGAA
CATGACTTTC 180

AGATGCTCTT TGCCCCTTGC TGTCATCAGT GTGGTGAATT CATCATTGGC
CGAGTTATCA 240
AAGCCATGAA TAACAGCTGG CATCCGGAGT GCTTCCGCTG TGACCTCTGC
CAGGAAGTTC 300
TGGCAGATAT CGGGTTTGTC AAGAATGCTG GGAGACACCT GTGTCGCCCC
TGTCATAATC 360
GTGAGAAAGC CAGA
374

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 492 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

CTTTGCATTT TACAGTAAGA ATCAAAGTCC CTTCAGTGTG CCTTTGTCAG
CTAATATGTG 60
ACCAGCAATG ACAACCTTGG GAGTATTTAT TAAATATTAT GCTATGAATA
TAGGCAACAC 120
AGAACAGGGT TTGCAGTATA GCGTCTTGAT GCTAAATTCT CATATACCTC
TACACGAGAA 180
ATATGGAGGA GAAAAACAAG CATTTACATA TATTCTTCGT CACTTTGAAG
ATGCATGACC 240
TGAACTCGAC TGCTTGTGTT TGTTTACATA TCAGGCATAC CCAGGCATCT
CCTGCAGCCA 300
GAGGTTCCAT TGCTGTCTTT GCTCAGTCCT CTTTTAAAAT ATGAATTAGT
GGACAGGCAC 360
GGTGCCTCAC ACCTGTAATC CCAGCACTTT GGGAGGTCGA GGCAGGTGGA
TCACGAGGTC 420
AGGAGATCAA GACCATCCTG GCTACCACTG AAACCCCATC TCTACTACAA
AAAAAAAAAA 480
AAAAAACTCG AG
492

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

Ser Gln Ile Cys Glu Leu Val Ala His Glu Thr Ile Ser Phe Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

Xaa Xaa Xaa Xaa Xaa Ser Ile Leu Asp Glu Val Ile Arg Gly Thr
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

Val Val Lys Thr Tyr Leu Ile Ser Ser Ile Pro Gln Gly Ala Phe Asn
1 5 10 15
Tyr Lys Tyr Thr Ala
20

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

Val Val Lys Thr Tyr Leu Ile Ser Ser Ile Pro Leu Gln Ala Phe Asn
1 5 10 15
Tyr Lys Tyr Thr Ala
20

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

Xaa Ala Lys Lys Phe Leu Asp Ala Glu His Lys Leu Asn Phe Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

Xaa Xaa Xaa Lys Ile Lys Lys Phe Ile Gln Glu Asn Ile Phe Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

Xaa Lys Val Lys Val Gly Val Asn Gly Phe Gly Arg Ile Gly Arg Leu
1 5 10 15

Val Thr

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

Xaa Tyr Gln Tyr Pro Ala Leu Thr Xaa Glu Gln Lys Lys Glu Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

Xaa Pro Ala Val Tyr Phe Lys Xaa Xaa Phe Leu Asp Xaa Asp
1 5 10

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

Xaa Pro Ala Val Tyr Phe Lys Glu Gln Phe Leu Asp Gly Asp Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

Xaa Xaa Val Ala Val Leu Xaa Ala Ser Xaa Xaa Ile Gly Gln Pro Leu
1 5 10 15
Ser Leu

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

Val Val Lys Thr Tyr Leu Ile Ser Xaa Ile Pro Leu Gln Gly Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

Xaa Xaa Lys Thr Tyr Leu Ile Ser Ser Ile Pro Leu Gln Gly Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

Met Asp Ile Pro Gln Thr Lys Gln Asp Leu Glu Leu Pro Lys Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1497 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

GGAGGGCAGA GATATCCAGT AGACAGAAGA TCTTGGACCC CAGGAAGTAT

ATTGGAAGAG 60
GTGCCTGGAG AAATGGATGC TAGAAGAAAA CACTGGAAGG AGAATATGTT
TACTCCTTTT 120
TTTAGTGCAC AAGATGTTCT AGAAGAGACT TCTGAGCCTG AATCTTCTTC
TGAACAAACG 180
ACTGCAGATA GCAGCAAGGG AATGGAAGAA ATTTATAATT TGTCCAGTAG
AAAGTTTCAG 240
GAAGAAAGTA AATTTAAGAG GAAAAAATAT ATTTTCCAAC TAAATGAAAT
AGAACAAGAA 300
CAAAATTTAA GAGAGAACAA GAGAAACATT TCAAAGAATG AAACAGACAC
AAATTCTGCA 360
TCCTATGAAT CATCTAATGT GGATGTTACA ACAGAAGAAA GCTTTAACAG
CACAGAAGAT 420
AACTCTACCT GCAGTACAGA TAACTTACCA GCTCTACTAA GACAAGACAT
AAGAAAGAAA 480
TTTATGGAAA GAATGTCTCC AAAACTTTGC CTGAATCTTT TGAATGAAGA
ACTGGAAGAA 540
CTTAATATGA AATACAGAAA AATAGAAGAG GAATTTGAAA ATGCTGAAAA
AGAACTTTTG 600
CACTACAAAA AAGAAATATT CACAAAACCC CTAAATTTTC AAGAAACAGA
GACGGATGCT 660
TCAAAAAGTG ACTATGAACT TCAAGCTTTA AGAAATGACC TGTCTGAAAA
AGCAACAAAT 720
GTAAAAAACT TAAGTGAACA GCTCCAGCAA GCCAAAGAAG TCATCCACAA
ATTGAACCTA 780
GAGAACAGAA ATTTAAAAGA AGCTGTTAGG AAGTTAAAGC ATCAAACCGA
GGTTGGAAAT 840
GTGCTCCTAA AAGAAGAAAT GAAATCATAT TATGAATTAG AAATGGCAAA
GATCCGCGGA 900
GAGCTCAGTG TCATCAAGAA TGAACTGAGA ACTGAGAAGA CCCTACAAGC
AAGAAATAAC 960
AGAGCCTTGG AGTTGCTTAG AAAATACTAT GCTTCTTCAA TGGTAACATC
ATCAAGTATC 1020
CTTGACCACT TTACTGGGGA TTTTTTTTAA AACTTAAAAA AATCCTTCCA
GTAGGCAAGT 1080
CATTGAGCCA AATCAGTGTT TATTGTATTT TCTTTGCGTA TTACTTAAAA
TATATGTAAT 1140
AGGATGTTAT TTTCATTTTC AGTAAATCAC AGTATCTATA AAACATATAC
ATGTTTCCAA 1200
GCTTCTGCTT TCTCTTTCTG ATGAAGTTAT TGCAGGAATA CAAATGGAAA
CGAAGCTTTG 1260
GAAATCTCAT ATCAGAGTGT GTGTGTGTGT GTGTGTGTGT GTGTGTACAC
ACACACATAT 1320
ATTCACTCAA AAACACATAA TGATTCACCA AATCATTTAT GAATACAAAT
CAGCAATTTT 1380

GTGATCTCGT AAGCAAATAT GTCTTTGGCA CGTGAATATT TTTCCATCTG
TGTTCATTGA 1440
TGTTAACAAT AAAAATCTTG TTTATGTGTA TAAGCCTAAA AAAAAAAAAA AAAAAAA
1497

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1050 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

ACCAGCTCTA CTAAGACAAG ACATAAGAAA GAAATTTATG GAAAGAATGT
CTCCAAAACT 60
TTGCCTGAAT CTTTTGAATG AAGAACTGGA AGAACTTAAT ATGAAATACA
GAAAAATAGA 120
AGAGGAATTT GAAAATGCTG AAAAAGAACT TTTGCACTAC AAAAAAGAAA
TATTCACAAA 180
ACCCCTAAAT TTTCAAGAAA CAGAGACGGA TGCTTCAAAA AGTGACTATG
AACTTCAAGC 240
TTTAAGAAAT GACCTGTCTG AAAAAGCAAC AAATGTAAAA AACTTAAGTG
AACAGCTCCA 300
GCAAGCCAAA GAAGTCATCC ACAAATTGAA CCTAGAGAAC AGAAATTTAA
AAGAAGCTGT 360
TAGGAAGTTA AAGCATCAAA CCGAGGTTGG AAATGTGCTC CTAAAAGAAG
AAATGAAATC 420
ATATTATGAA TTAGAAATGG CAAAGATCCG CGGAGAGCTC AGTGTCATCA
AGAATGAACT 480
GAGAACTGAG AAGACCCTAC AAGCAAGAAA TAACAGAGCC TTGGAGTTGC
TTAGAAAATA 540
CTATGCTTCT TCAATGGTAA CATCATCAAG TATCCTTGAC CACTTTACTG
GGGATTTTTT 600
TTAAAACTTA AAAAAATCCT TCCAGTAGGC AAGTCATTGA GCCAAATCAG
TGTTTATTGT 660
ATTTTCTTTG CGTATTACTT AAAATATATG TAATAGGATG TTATTTTCAT
TTTCAGTAAA 720
TCACAGTATC TATAAAACAT ATACATGTTT CCAAGCTTCT GCTTTCTCTT

TCTGATGAAG 780
TTATTGCAGG AATACAAATG GAAACGAAGC TTTGGAAATC TCATATCAGA
GTGTGTGTGT 840
GTGTGTGTGT GTGTGTGTGT ACACACACAC ATATATTCAC TCAAAAACAC
ATAATGATTC 900
ACCAAATCAT TTATGAATAC AAATCAGCAA TTTTGTGATC TCGTAAGCAA
ATATGTCTTT 960
GGCACGTGAA TATTTTTCCA TCTGTGTTCA TTGATGTTAA CAATAAAAAT
CTTGTTTATG 1020
TGTATAAGCC TAAAAAAAAA AAAAAAAAAA
1050

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 325 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

Met Asp Ala Arg Arg Lys His Trp Lys Glu Asn Met Phe Thr Pro Phe
1 5 10 15
Phe Ser Ala Gln Asp Val Leu Glu Glu Thr Ser Glu Pro Glu Ser Ser
20 25 30
Ser Glu Gln Thr Thr Ala Asp Ser Ser Lys Gly Met Glu Glu Ile Tyr
35 40 45
Asn Leu Ser Ser Arg Lys Phe Gln Glu Glu Ser Lys Phe Lys Arg Lys
50 55 60
Lys Tyr Ile Phe Gln Leu Asn Glu Ile Glu Gln Glu Gln Asn Leu Arg
65 70 75 80
Glu Asn Lys Arg Asn Ile Ser Lys Asn Glu Thr Asp Thr Asn Ser Ala
85 90 95
Ser Tyr Glu Ser Ser Asn Val Asp Val Thr Thr Glu Glu Ser Phe Asn
100 105 110
Ser Thr Glu Asp Asn Ser Thr Cys Ser Thr Asp Asn Leu Pro Ala Leu
115 120 125
Leu Arg Gln Asp Ile Arg Lys Lys Phe Met Glu Arg Met Ser Pro Lys
130 135 140
Leu Cys Leu Asn Leu Leu Asn Glu Glu Leu Glu Glu Leu Asn Met Lys
145 150 155 160
Tyr Arg Lys Ile Glu Glu Glu Phe Glu Asn Ala Glu Lys Glu Leu Leu
165 170 175
His Tyr Lys Lys Glu Ile Phe Thr Lys Pro Leu Asn Phe Gln Glu Thr
180 185 190
Glu Thr Asp Ala Ser Lys Ser Asp Tyr Glu Leu Gln Ala Leu Arg Asn
195 200 205
Asp Leu Ser Glu Lys Ala Thr Asn Val Lys Asn Leu Ser Glu Gln Leu
210 215 220

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Gln Gln Ala Lys Glu Val Ile His Lys Leu Asn Leu Glu Asn Arg Asn
225                 230                 235                 240
Leu Lys Glu Ala Val Arg Lys Leu Lys His Gln Thr Glu Val Gly Asn
                245                 250                 255
Val Leu Leu Lys Glu Glu Met Lys Ser Tyr Tyr Glu Leu Glu Met Ala
            260                 265                 270
Lys Ile Arg Gly Glu Leu Ser Val Ile Lys Asn Glu Leu Arg Thr Glu
        275                 280                 285
Lys Thr Leu Gln Ala Arg Asn Asn Arg Ala Leu Glu Leu Leu Arg Lys
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Tyr Tyr Ala Ser Ser Met Val Thr Ser Ser Ser Ile Leu Asp His Phe
305                 310                 315                 320
Thr Gly Asp Phe Phe
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(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 702 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

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AGGTGCCAGA NATGGCTGTG CCGGANGTGC GGCTTCCAGA NGTAGACTGC CCANAGTGTC    240
AGAGATGAAA CTCCCAAAGG TGCCAGAAAT GCTGTGCCGG AAGTNCCGCT TCCAGAAGTA    300
CAGCTGCTGA AAGTGTCGGA GATNAAACTC CCAAAGGTGC CANAGATGGC TGTGCCGGAN    360
GTGCGGCTTC CAGANGTACA GCTGCCGAAT GTGTCAAGAA TGAAACTCCC ANAAGTGTCA    420
NANGTGGCTG TGCCANAAGT GCGGCTTCCA GANGTGCAGC TGCCGAATGT GCCAGAANAT    480
NAAAGTCCCT GANATGAAGC TTCCAANGGT GCCTGAAATG AAACTTCCTG AAGATGAAAC    540
TCCCTGAAAT TGCNNCTCCC GAAAGGTGCC CAAAATGGCC GTGCCCGATN TGCCCTCCCA    600
GAANTTCNNC TTCCNAAANT CCAGAAATAA NCNCCCTGAA ATGAAACCCC CGAGGTGAAC    660
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(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 688 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

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NTTTTTTTNN CNCNTNTNNN TACTTCCAAA TTATTTTATT CACATGGCTT GGTGGGGTAC    180
```

AGGCACTCCT GCCAAAAANA CAGGAACAGG CCTCCCTGCC ANCCCTGNTC ATTCACCACC 240
TCCCGGCCCT CTTAGGGTTN GTGCTANTTA NTCACACACA CACAGCGAAG GGGTAAAAAA 300
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CAATCCACCT CTTCCTGNTC CCACTCCCAC TCCGGGCCTN GGGGCTTAGG GACCCCTGGG 480
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GCCCCCAAAA GCTTTAAAAG GGGCCCTCAN NCCTACCTTT GNCAANCCGG AACCNGAACC 600
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(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 814 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

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ATAACTCTGG ACTTCTCAAA NATGGTGATG CCCAGTCACT TAAGGAACAC CTTATTGATG 240
AATTGGATTA CATACTGTTG CCAACTGAAG GTTGGAATAA ACTTGTCAGC TGGTACACAT 300
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ACTGCAAAGT ANAAGTATAT CTCACAGAAT TGAAGCTATG TGAAAATGGA AACATGAATA 420
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GTAACACATT TGAACCACTG AATAAACCAG ACAGCACCAT TCAGGATGCT GGTTTATACC 600
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CTACTCCTAA GTCCCCAGGT GCATCCAATT TTTCAACTTT ACCAAAGATC TCTCCTTCAT 720
CTCTATCAAA TTNATTATTA CAACATGAAC AACAGAAATG TGAAAAACTC AAATTACTGT 780
CTTCCATCAT ATACCGCTTA TAAGAACTAT GATT 814

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 966 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

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TGTTTCACTT CAAGTACTGC ACAAGTTAAA ATCTGATAAA GGATTTACAT TCGGTTATCT 180
GAAACTCCCC ATCTCANACT TTTGTTTTAA TGTGGTGGGT AACTTCATCA TTTCCATAGA 240
TACCACCAGC AGGAAAGTGT CTCTTTTATG GCTTCTAGGA CTTTCATTAG TTAGTGTGCA 300
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CACTGAGAAG TGTCTTGTCT CTGGTAAAAN ARTACATATG CTGCTTGTGG ACACAATTTG 480
GTCTTCANAT GCAGTGGAGA CNCTACTGTC ATCAAAATAG TACCATTTNC CATCATCTTT 540
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AATCANATTA TAGCGGCAAG GACCTGCATT TGGATTAATT AANAATTCCG ACATATCCAA 660
GTCATTGATA GGAAAATCAA CTAAGGTATC CAACTTGTCT CTCATGTATC GACTGTAANA 720
AAATCGCTTG AGATGTACTA CAAGTACTGG AGGCAGGGAC CATAAATCCA ATTTCTTTGT 780
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(2) INFORMATION FOR SEQ ID NO:65

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1020 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

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CACGTTCCAG AGCATCGCGG GCCTGGAGGA AAACTTCCAC AAGGAGATGA GCAAGCTCAA 240
CCAGAACCTC AATGATGTGC TGGTCGGCCT GGAGAAGCAA CACGGGAGCA ACACCTTCAC 300
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TCCCAAAGCT TCTTCTTTTC CCCTGGCTTG TTTTCNTTTN GGGNTTGGGN AAAAAAACCT 780
TTTCCCCCCA AGCCAAAAAN TTGGTTNNAA AATTTGGGGC CNCCCCCNNT TGGAAAAAGG 840
GGGGGNGGGC CNAATTTTGG GGGGCCCNGG GCCCCCTTTG GGAAACCTNG CCCCCCCAAG 900
GTTTTCCATN NTTTCAANGG GTTAAAGGGC CNACANAAAA AAACCCGGGC CCTTGAACCC 960
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(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 928 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

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CNCTCCTTCN CGCCCATGAA CCANCCTTCA TCCTGCTCTT TCANGGTTCT GGAAAGGGGG    720
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GGGGGGGGTT CCAAANCGCC CCGGGGCCCC ACTTGGCCCG CCCTNCCCAC GGGNTGCCNN    900
TTCCNCNANT TTCTTTGGGG NAAAGGTC                                       928
```

CLAIMS

1. A polypeptide comprising an immunogenic portion of a prostate protein having a partial sequence selected from the group consisting of SEQ ID NOS: 2, 4, 5, 6, 7 and 8, or a variant of said protein that differs only in conservative substitutions and/or modifications.

2. A polypeptide comprising an immunogenic portion of a prostate protein or a variant of said protein that differs only in conservative substitutions and/or modifications wherein said protein comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of sequences recited in SEQ ID NOS: 11, 13-19, 58, 59 and 61-64, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID NOS: 11, 13-19, 58, 59 and 61-64, or a complement thereof under moderately stringent conditions.

3. A DNA molecule comprising a nucleotide sequence encoding the polypeptide of claims 1 or 2.

4. An expression vector comprising the DNA molecule of claim 3.

5. A host cell transformed with the expression vector of claim 4.

6. The host cell of claim 5 wherein the host cell is selected from the group consisting of *E. coli*, yeast and mammalian cell lines.

7. A pharmaceutical composition comprising the polypeptide of claims 1 or 2 and a physiologically acceptable carrier.

8. A vaccine comprising the polypeptide of claims 1 or 2 and a non-specific immune response enhancer.

9. The vaccine of claim 8 wherein the non-specific immune response enhancer is an adjuvant.

10. A vaccine comprising a DNA molecule and a non-specific immune response enhancer, the DNA molecule comprising a nucleotide sequence encoding the polypeptide of claims 1 or 2.

11. The vaccine of claim 10 wherein the non-specific immune response enhancer is an adjuvant.

12. A pharmaceutical composition for the treatment of prostate cancer comprising a polypeptide and a physiologically acceptable carrier, the polypeptide comprising an immunogenic portion of a prostate protein having a partial sequence selected from the group consisting of SEQ ID NOS: 1, 3, 20, 21, 25-31 and 44-57.

13. A vaccine for the treatment of prostate cancer comprising a polypeptide and a non-specific immune response enhancer, the polypeptide comprising an immunogenic portion of a prostate protein having a partial sequence selected from the group consisting of SEQ ID NOS: 1, 3, 20, 21, 25-31 and 44-57.

14. The vaccine of claim 13 wherein the non-specific immune response enhancer is an adjuvant.

15. A method for inhibiting the development of prostate cancer in a patient, comprising administering to the patient an effective amount of the pharmaceutical composition of claims 7 or 12.

16. A method for inhibiting the development of prostate cancer in a patient, comprising administering to the patient an effective amount of the vaccine of claims 8, 10 or 12.

17. A method for detecting prostate cancer in a patient, comprising:

(a) contacting a biological sample obtained from a patient with a binding agent which is capable of binding to the polypeptide of claims 1 or 2; and

(b) detecting in the sample a protein or polypeptide that binds to the binding agent, thereby detecting prostate cancer in the patient.

18. The method of claim 17 wherein the binding agent is a monoclonal antibody.

19. The method of claim 17 wherein the binding agent is a polyclonal antibody.

20. A method for monitoring the progression of prostate cancer in a patient, comprising:

(a) contacting a biological sample obtained from a patient with a binding agent that is capable of binding to the polypeptide of claims 1 or 2;

(b) determining in the sample an amount of a protein or polypeptide that binds to the binding agent;

(c) repeating steps (a) and (b); and

(d) comparing the amount of polypeptide detected in steps (b) and (c) to monitor the progression of prostate cancer in the patient.

21. A method for detecting prostate cancer in a patient, comprising:

(a) contacting a biological sample obtained from a patient with a binding agent which is capable of binding to a polypeptide, the polypeptide comprising an

immunogenic portion of a prostate protein having a partial sequence selected from the group consisting of SEQ ID NOS: 1, 3, 20, 21, 25-31 and 44-57; and

(b) detecting in the sample a protein or polypeptide that binds to the binding agent, thereby detecting prostate cancer in the patient.

22. The method of claim 21 wherein the binding agent is a monoclonal antibody.

23. The method of claim 21 wherein the binding agent is a polyclonal antibody.

24. A method for monitoring the progression of prostate cancer in a patient, comprising:

(a) contacting a biological sample obtained from a patient with a binding agent that is capable of binding to a polypeptide, the polypeptide comprising an immunogenic portion of a prostate protein having a partial sequence selected from the group consisting of: SEQ ID NOS: 1, 3, 20, 21, 25-31 and 44-57;

(b) determining in the sample an amount of a protein or polypeptide that binds to the binding agent;

(c) repeating steps (a) and (b); and

(d) comparing the amount of polypeptide detected in steps (b) and (c) to monitor the progression of prostate cancer in the patient.

25. A monoclonal antibody that binds to the polypeptide of claims 1 or 2.

26. A monoclonal antibody according to claim 25, for use in the manufacture of a medicament for inhibiting the development of prostate cancer.

27. The monoclonal antibody of claim 26 wherein the monoclonal antibody is conjugated to a therapeutic agent.

28. A method for detecting prostate cancer in a patient, comprising:

(a) contacting a biological sample from a patient with at least two oligonucleotide primers in a polymerase chain reaction, wherein at least one of the oligonucleotide primers is specific for a DNA molecule selected from the group consisting of SEQ ID NOS: 9-19, 22-24, 32-43, 58, 59 and 61-64; and

(b) detecting in the sample a DNA sequence that amplifies in the presence of the oligonucleotide primer, thereby detecting prostate cancer.

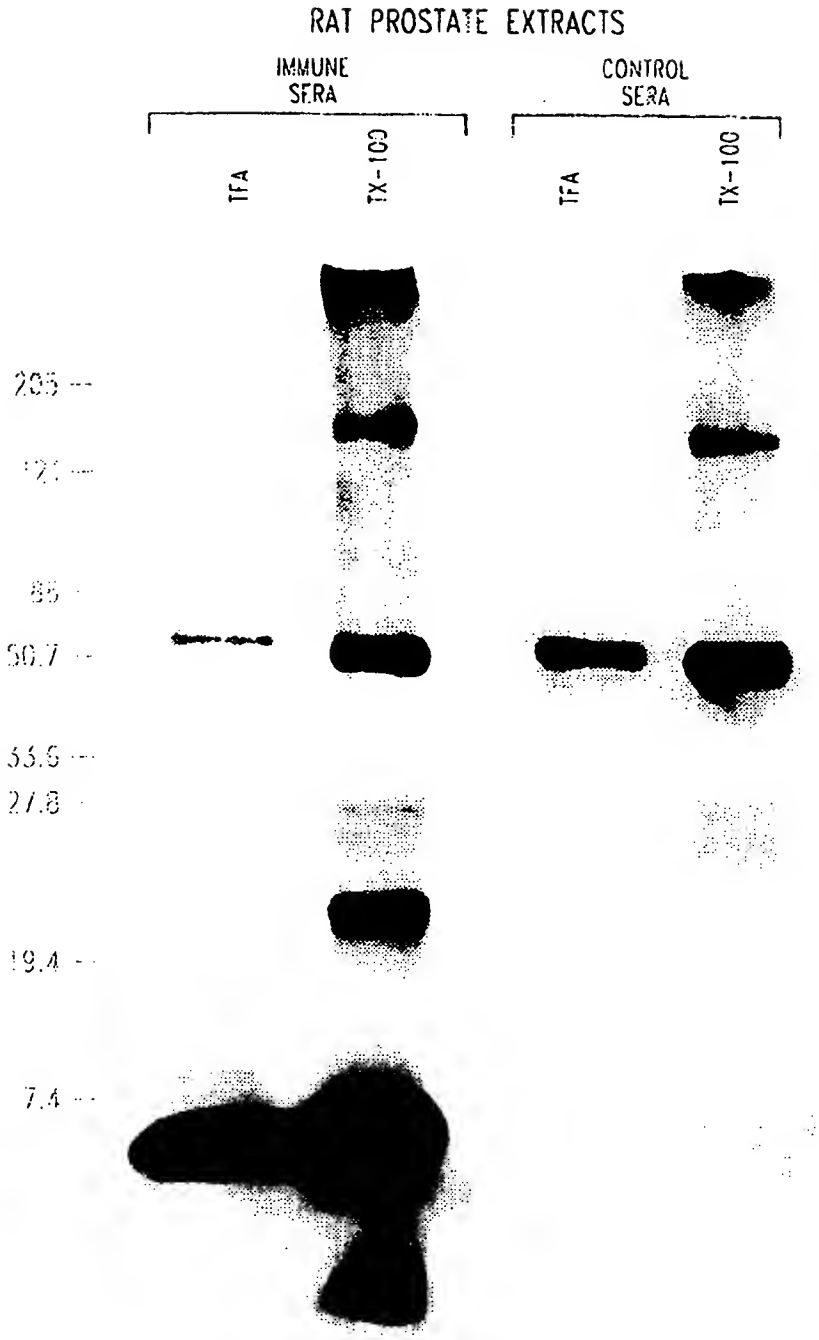
29. The method of claim 28, wherein at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a DNA molecule selected from the group consisting of SEQ ID NOS: 9-19, 22-24, 32-43, 58, 59 and 61-64.

30. A method for detecting prostate cancer in a patient, comprising:

(a) contacting a biological sample from the patient with at least one oligonucleotide probe specific for a DNA molecule selected from the group consisting of SEQ ID NOS: 9-19, 22-24, 32-43, 58, 59 and 61-64; and

(b) detecting in the sample a DNA sequence that hybridizes to the oligonucleotide probe, thereby detecting prostate cancer.

31. The method of claim 30 wherein the probe comprises at least about 15 contiguous nucleotides of a DNA molecule selected from the group consisting of SEQ ID NOS: 9-19, 22-24, 32-43, 58, 59 and 61-64.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IMMUNE SERA
CONTROL SERA
TFA
TX-100
TFA
TX-100
205
121
85
50.7
33.9
27.8
19.4
7.4

Fig. 1

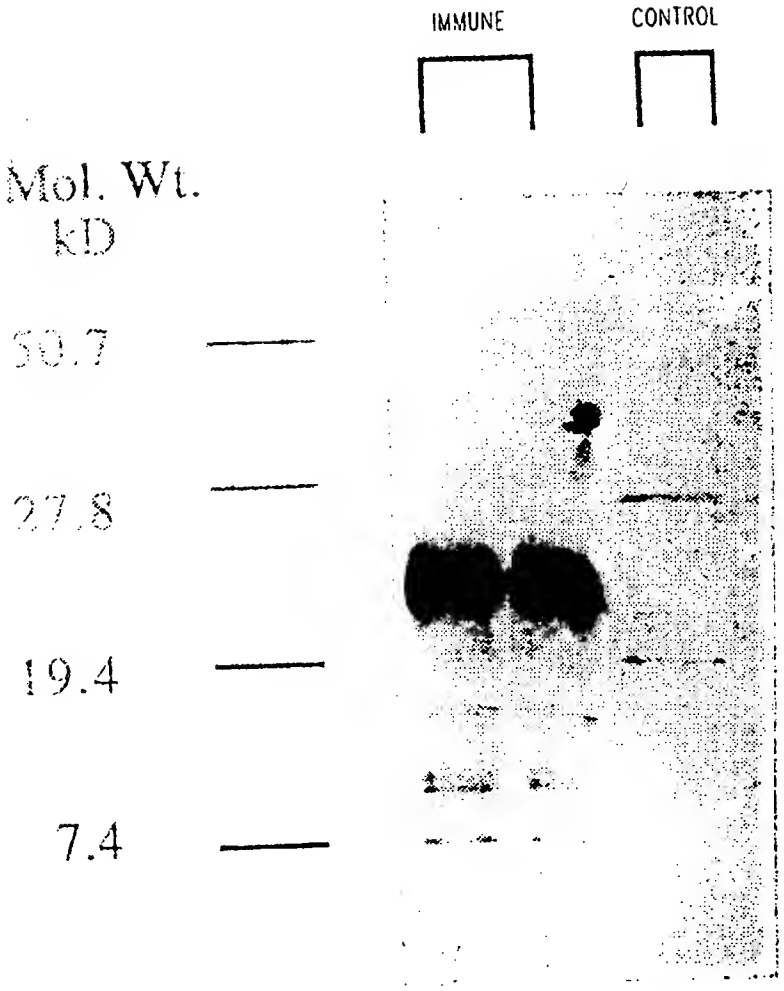
RAT PROSTATE EXTRACT
NON-REDUCED SDS-PAGE
IMMUNE
CONTROL
Mol. Wt.
kD
50.7
27.8
19.4
7.4

Fig. 2

HUMAN

Fig. 3B

RAT

Fig. 3A

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C12N 15/12, C07K 14/705, A61K 38/17, G01N 33/68, C12Q 1/68, C07K 16/18

A3

(11) International Publication Number: WO 99/18210

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(21) International Application Number: PCT/US98/21166

(22) International Filing Date: 7 October 1998 (07.10.98)

(30) Priority Data:

08/946,026	7 October 1997 (07.10.97)	US
09/102,679	23 June 1998 (23.06.98)	US

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(74) Agents: MAKI, David, J. et al.; Seed and Berry LLP, 6300 Columbia Center, 701 Fifth Avenue, Seattle, WA 98104–7092 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

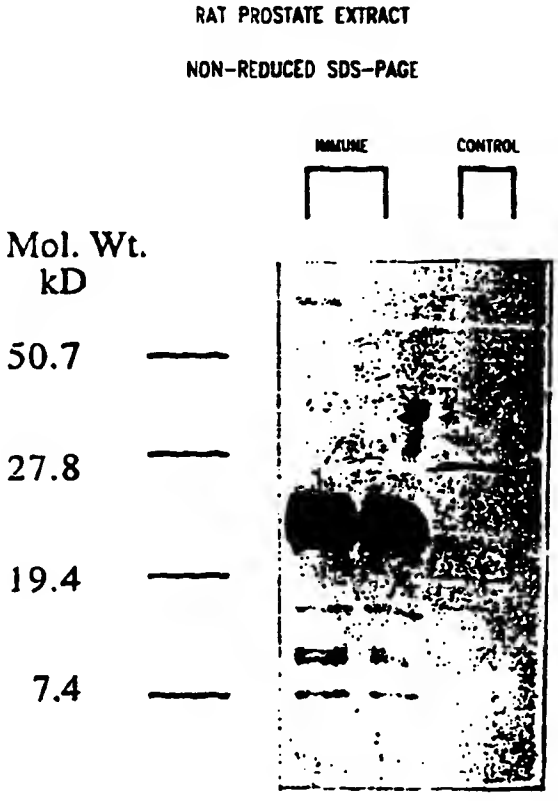
Published
With international search report.

(88) Date of publication of the international search report:
5 August 1999 (05.08.99)

(54) Title: COMPOUNDS AND METHODS FOR IMMUNOTHERAPY AND IMMUNODIAGNOSIS OF PROSTATE CANCER

(57) Abstract

Compounds and methods for treating and diagnosing prostate cancer are provided. The inventive compounds include polypeptides containing at least a portion of a prostate protein. Vaccines and pharmaceutical compositions for immunotherapy of prostate cancer comprising such polypeptides or DNA molecules encoding such polypeptides are also provided. The inventive polypeptides may also be used to generate antibodies useful for the diagnosis and monitoring of prostate cancer. Nucleic acid sequences for preparing probes, primers, and polypeptides are also provided.



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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/21166

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C07K14/705 A61K38/17 G01N33/68 C12Q1/68
C07K16/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C12N A61K G01N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 33909 A (CORIXA CORP) 18 September 1997 see the whole document ---	1-11, 15-20, 25-31
X	HAWKINS T L ET AL.: "Genomic sequence from Human 13 (accession number AC000403)" EMBL DATABASE,9 April 1997, XP002094678 Heidelberg, Germany see nucleotides 52780-52920 see abstract ---	3-6, 28-31
P,X	CHEN E ET AL.: "Homo sapiens Chromosome X clone bWXD178 (accession number AC004409)" EMBL DATABASE,16 March 1998, XP002094679 Heidelberg, Germany see nucleotides 35860-37310 see abstract -----	3-6, 28-31

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 February 1999	03.06.99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Oderwald, H

3

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US 98/21166

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons

1 [X] Claims Nos
because they relate to subject matter not required to be searched by this Authority, namely
Remark: Although claims 15 and 16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3 [ ] Claims Nos
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows

see continuation-sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.

4 [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos

1,12-14,21-24 all complete; 2-11,15-20,25-31 all partially

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest

[ ] No protest accompanied the payment of additional search fees

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1, 12-14, 21-24 all complete; 2-11, 15-20, 25-31 all partially

Prostate proteins and DNA encoding said protein (SEQ ID NO: 1-59), expression vector, host cell, pharmaceutical composition and vaccine comprising said protein and DNA. Antibodies against said protein, use of said antibodies in a method for detecting prostate cancer, in a method for monitoring the progression of prostate cancer and in the manufacture of a medicament. Method for detecting prostate cancer using primers and probes derived from said DNA.

2. Claims: 2-11, 15-20, 25-31 all partially

same as in invention 1 but comprising SEQ ID NO: 61 and 62.

3. Claims: 2-11, 15-20, 25-31 all partially

same as in invention 1 but comprising SEQ ID NO: 63 and 64.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/21166

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9733909 A	18-09-1997	AU 2329597 A	01-10-1997
		CA 2249742 A	18-09-1997
		EP 0914335 A	12-05-1999
		NO 984229 A	13-11-1998